CLINICAL PRACTICE GUIDELINES

Antithrombotic Therapy

List of Contributors

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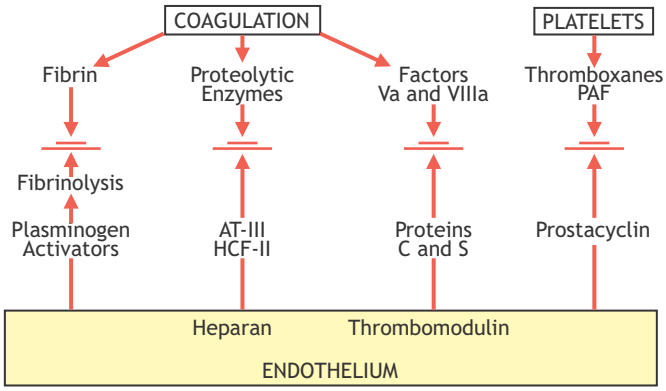
1. Introduction

Arterial, cardiac and venous thromboembolism, are major causes of death and disability. Major manifestations are,

- Coronary thrombosis (presenting as sudden cardiac death or acute coronary syndrome) which frequently results in death or in disabling heart failure.
- Stroke, which again is often fatal or disabling: about 85% of strokes are due to thromboembolism (from the heart, aorta, neck arteries or, rarely, leg veins) and about 15% are due to intracranial bleeding (including that associated with anticoagulant therapy).
- Limb ischaemia, which is often due to thromboembolism from the heart, aorta or arteries to the lower limbs.
- Deep vein thrombosis of the lower limb (DVT) or its sequel, pulmonary embolism (PE).

The prothrombotic and antithrombotic factors of the hemostatic system are normally finely balanced, opposing mechanisms. To protect against vascular damage and the risk of bleeding to death, the prothrombotic system is poised to rapidly form a thrombus to limit any potential hemorrhage. As long as the vascular endothelium is intact, at least four different mechanisms keep the blood flowing; antiaggregatory (via prostacyclin), vasodilatory (via nitric oxide), fibrinolytic (via tPA) and antithrombotic (via thrombomodulin).



The formation of thrombus occurs in three steps:

(1) exposure of the circulating blood to a thrombogenic surface, such as damaged vascular endothelium resulting from a ruptured atherosclerotic plaque,

(2) a sequence of platelet-related events involving platelet adhesion, platelet activation, and platelet aggregation (Fig. 9-3), with release of substances that further promote aggregation and cause vasoconstriction, and

(3) triggering of the clotting mechanism. Thrombin plays an important role in the formation of fibrin, which cross-links to form the backbone of the thrombus. Thrombin is in itself a very powerful stimulator of platelet adhesion and aggregation.

Once formed, the thrombus may be broken down by plasmin-stimulated fibrinolysis. Current antithrombotic medications include platelet inhibitors, anticoagulants, and fibrinolytic agents. The typical arterial thrombus has a white head due to platelet aggregation, and a red tail due to stasis beyond the lesion.

The three main types of agent discussed here act at different stages of the thrombotic process.

- First, platelet inhibitors act on arterial thrombi and help prevent consequences such as myocardial infarction and transient ischemic attacks (TlAs).
- Second, anticoagulants given for acute conditions (e.g., heparin) limit the further formation of fibrin and when given for chronic conditions (e.g., warfarin) help prevent thromboembolism from a dilated left atrium or from veins such as those in the legs.
- Third, fibrinolytic agents are most useful in the clinical syndromes of acute arterial thrombosis and occlusion, such as myocardial infarction and peripheral arterial thrombosis.

The different sites of action of these three types of agent mean that combination therapy can be beneficial. For example, fibrinolytic agents are used together with antiplatelet agents and anticoagulants in the management of acute myocardial infarction.

ANTIPLATELET THERAPY

Antiplatelet therapy is clearly effective in reducing death in acute myocardial infarction or acute ischaemic stroke and in the prevention of serious vascular events when given as secondary prophylaxis to patients with clinical evidence of arterial disease. It is also effective in prevention
of stroke in selected patients with heart valve disease, atrial fibrillation and in primary prevention of myocardial infarction in men with multiple risk factors. Despite this clear evidence of efficacy, audit studies have shown that many such patients do not receive aspirin from their general practitioners or hospital doctors.

ANTICOAGULANT THERAPY

Anticoagulant therapy, usually with heparin injections short term and/or oral anticoagulants (usually warfarin) long term, is also clearly effective in prevention of serious vascular events when given as prophylaxis to high-risk patients, or as treatment of acute arterial or venous thrombosis. As in the case of antiplatelet therapy, many high-risk patients do not receive anticoagulant prophylaxis or treatment. However, full-dose anticoagulation is also a common cause of major internal bleeding, including intracranial, gastrointestinal or retroperitoneal haemorrhage, which can be fatal. It is therefore important to select patients most likely to benefit from anticoagulant therapy (i.e. those in whom the risk of major thromboembolic events exceeds the risk of major bleeding); and to minimise both thromboembolic and haemorrhagic morbidity and mortality during anticoagulant therapy.

Approaches to the latter include:

- use of optimal target effect and range for unfractionated heparin and warfarin
- patient and laboratory monitoring
- patient education
- effective communication between patients, general practitioners, hospital doctors, anticoagulant clinics, haematology laboratories, and other relevant health care professionals (e.g. pharmacists, dentists).

With the increasing use of heparin in hospitals, and the increasing use of long-term warfarin in outpatients it is important to ensure that the considerable potential of anticoagulant prophylaxis to reduce thromboembolic mortality is not only assured by clinical audit of use and monitoring, but is also not outweighed by increased morbidity and mortality due to drug-induced bleeding.

THROMBOLYTIC THERAPY

As distinct from antithrombotic therapy with aspirin, heparin or warfarin, which prevents or reduces formation of platelet-fibrin thrombi, thrombolytic (fibrinolytic) agents lyse fibrin thrombi by activating endogenous plasminogen to plasmin, which dissolves fibrin. Short term thrombolytic therapy with streptokinase, anistreplase, or tissue plasminogen activator (alteplase) has been shown to significantly reduce mortality and when given to selected patients with evolving acute myocardial infarction (MI).

2. Antithrombotic therapy in specific situations

Ischemic Heart Disease

1. Patients with acute ST-elevation myocardial infarction

Thrombolysis and adjunctive therapy

Thrombolysis with streptokinase

- All patients with ischemic symptoms characteristic of acute MI for < 12 h who have ST-segment elevation or left bundle-branch block on the ECG should receive any approved fibrinolytic therapy unless they have contraindications (grade A).

- Patients with prior intracranial hemorrhage, ischaemic stroke within the past 3 months, or closed head trauma should not be given fibrinolytic therapy (grade A).

- All patients with acute MI who are candidates for fibrinolytic therapy should receive it within 30 min after arrival to the hospital (grade A).

- For high risk patients with ongoing symptoms characteristic of acute MI or haemodynamic compromise and duration of 12 to 24 h who have ST-segment elevation or left bundle-branch block on the ECG, fibrinolytic therapy should be considered (grade C).

Adjunctive treatment with antithrombotic agent in patients receiving fibrinolysis for AMI

Adjunctive treatment with aspirin: All patients should chew and swallow nonenteric-coated aspirin (150 to 300 mg po 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 150 mg/d) (grade A).

Adjunctive treatment with clopidogrel: All patients should be given **clopidogrel** for at least 9 months(a loading dose of 300mg followed by 75 mg/d) (grade A).

Adjunctive treatment with UFH

For patients receiving streptokinase, administration of either IV UFH 5000 U
bolus followed by 1000 U/h for patients >80 kg and 800 U/kg for <80 kg or
subcutaneous UFH(12,500 U q12h) for 48 h is recommended (grade A).

For patients given streptokinase, administration of IV unfractionated heparin is recommended only if they are at high risk of systemic or venous thromboembolism (anterior MI, existing heart failure, previous embolus, atrial fibrillation, or left ventricular thrombus) (grade A).

Remark: Heparin should be given not earlier than 4 h after therapy and when the APTT is >70 s. The target APTT should be 50 to 70 s, and the infusion should continue for > 48 h.

2. Patients with Non-ST-Elevation Acute Coronary Syndromes (NSTE ACS)

Acute Management of Non-ST-Elevation Acute Coronary Syndromes (NSTE ACS)

Antiplatelet therapies

Aspirin

- For all patients presenting with an NSTE ACS, without a clear allergy to aspirin, immediate aspirin, 75 to 300 mg po, and then daily oral aspirin, 75 to 150 mg is recommended. (Grade A).

Thienopyridines

- For all NSTE ACS patients with an aspirin allergy, immediate treatment with clopidogrel, 300 mg oral bolus, followed by 75 mg/d indefinitely is recommended (Grade A).

- In all NSTE ACS patients in whom diagnostic catheterization will be delayed or when coronary bypass surgery will not occur until >5 days following coronary angiography, it is recommended that clopidogrel be administered immediately as bolus therapy (300 mg), followed by 75 mg/d for 9 to 12 months in addition to aspirin (Grade A).

- In NSTE ACS patients in whom angiography will take place rapidly (<24 h), clopidogrel should be commenced after the coronary anatomy has been determined (Grade A).

- For patients who have received clopidogrel and are scheduled for coronary bypass surgery, clopidogrel should be discontinued for 5 days prior to the scheduled surgery (Grade B).

Glycoprotein IIb/IIIa inhibitors

- In moderate- to high-risk patients presenting with NSTE ACS, either eptifibatide or tirofiban for initial (early) treatment in addition to treatment with aspirin and heparin is recommended(Grade A). In these moderate-to high-risk patients who are also receiving clopidogrel, eptifibatide or tirofiban as additional initial treatment (Grade B) is also recommended.

- For patients presenting with NSTE ACS, abciximab should not be used as initial treatment except when the coronary anatomy is known and Percutaneous Coronary Intervention (PCI) planned within 24 h (Grade A).

Antithrombin therapies

Unfractionated heparin

- For patients presenting with NSTE ACS, UFH over no heparin therapy for short-term use with antiplatelet therapies (Grade A) is recommended. UFH should be administered according to a weight-based dosing regimen and the APTT should be maintained between 50s and 70s (Grade A).

Low-molecular-weight heparin

- For the acute treatment of patients with NSTE ACS, LMWHs over UFH (Grade A) is recommended.
- Routine monitoring of the anticoagulant effect of the LMWHs is not recommended (Grade A).
- LMWHs should be continued during PCI treatment of the NSTE ACS patient when it has been started as the initial anticoagulant (Grade C).
- For patients receiving GP IIb/IIIa inhibitors as upstream treatment of NSTE ACS, LMWH is preferred over UFH as the anticoagulant of choice (Grade C).

3. Post MI and Post ACS

Antiplatelet therapies

In patients with ACSs with and without ST-segment elevation:

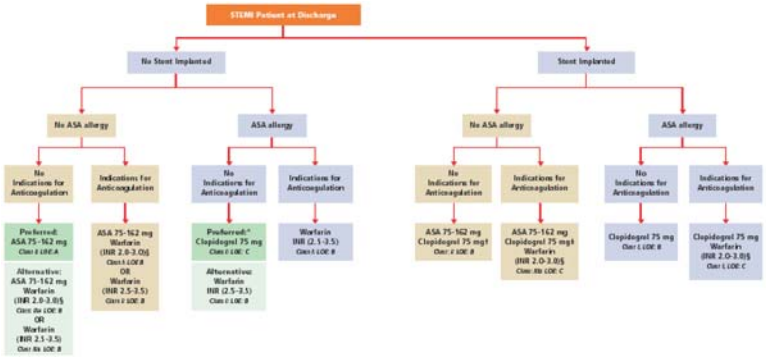
- Aspirin at initial doses from 150 to 300 mg, and then indefinite therapy, 75 to 150 mg/d (Grade A) is recommended.
- For patients with a history of aspirin-induced bleeding or with risk factors for bleeding, lower doses (<100 mg) of aspirin (Grade A) is recommended.
- For patients in whom aspirin is contraindicated or not tolerated, clopidogrel 75 mg/d for long-term administration (Grade A) is recommended.

Comparisons of antiplatelet and anticoagulant therapy and/or combinations of aspirin and warfarin trials

- In most health-care settings, for moderate- and low-risk patients with a myocardial infarction, aspirin alone over oral vitamin K antagonists (VKAs) plus aspirin (Grade C) is recommended.

- For high-risk patients with MI, including those with a large anterior MI, those with significant heart failure, those with intracardiac thrombus visible on echocardiography, and those with a history of a thromboembolic event, the combined use of moderate intensity (INR, 2.0 to 3.0) oral VKAs plus low-dose aspirin (<100 mg/d) for 3 months after the MI (Grade B) is suggested.

Long-Term Antithrombotic Therapy at Hospital Discharge After STEMI
Hospital Management (See Annexure 1)



4. Chronic, Stable CAD

Antiplatelet agents

- For all patients with chronic stable CAD, we recommend the administration of aspirin, 75 to 150 mg po (Grade A). It is recommended that all patients with stable CAD should be given aspirin 75 – 150mg /day (Grade 1A) and that this should be continued indefinitely (Grade 2C)

- For patients with stable chronic coronary disease with a risk profile indicating a high likelihood of development of AMI, long-term therapy with clopidogrel can be given in addition to aspirin (Grade C).

Vitamin K antagonists

· For patients with chronic CAD without prior MI, clinicians should not use long-term oral VKAs (Grade C).

5. Congestive Heart Failure With and Without CAD

VKA, aspirin

· In patients with CHF due to a nonischemic etiology, routine use of aspirin or oral VKAs is not recommended (Grade A).

· It is recommended that unless otherwise indicated, patients receive aspirin whether or not they are receiving ACEIs (Grade A).

6. Primary Prevention

Aspirin, VKA, or both

· For patients with at least moderate risk for a coronary event (based on age and cardiac risk factor profile with a 10-year risk of a cardiac event of >10%), 75 to 162 mg/d, over either no antithrombotic therapy or VKAs is recommended (Grade B).

· For patients at particularly high risk for events in whom INR can be monitored without difficulty, low-dose VKAs with a target INR of approximately 1.5 (Grade B) can be given.

7. Patients Undergoing PCI:

Oral Antiplatelet Therapy

Aspirin

· For patients undergoing PCI, pretreatment with aspirin, 75 to 300 mg (Grade A) is recommended.

- For long-term treatment after PCI, aspirin, 75 to 150 mg/d (Grade A) is recommended.

- For long-term treatment after PCI in patients who receive antithrombotic agents such as clopidogrel or warfarin, lower-dose aspirin, 75 to 100 mg/d (Grade B) is recommended.

Clopidogrel after stent placement

- For patients who undergo stent placement, the combination of aspirin and a thienopyridine derivative (clopidogrel) over systemic anticoagulation therapy (Grade A) is recommended.

- It is recommended that a loading dose of 300 mg of clopidogrel be given at least 6 h prior to planned PCI (Grade A). If clopidogrel is started <6 h prior to PCI, a 600-mg loading dose of clopidogrel (Grade C) should be given.

- Aspirin intolerant patients: For PCI patients who cannot tolerate aspirin, it is recommended that a loading dose of clopidogrel (300 mg) or ticlopidine (500 mg) be administered at least 24 h prior to planned PCI (Grade C).

Duration of thienopyridine therapy after stent placement

- After PCI, it is recommended that, clopidogrel (75 mg/d) is given in addition to aspirin for at least 9 to 12 months (Grade A).

- If ticlopidine is used in place of clopidogrel after PCI, it is recommended that ticlopidine is given for 2 weeks after placement of a bare metal stent in addition to aspirin (Grade A).

- In patients with low atherosclerotic risk, such as those with isolated coronary lesions, it is recommended that clopidogrel for at least 2 weeks after placement of a bare metal stent (Grade A), for 2 to 3 months after placement of a sirolimus-eluting stent (Grade B), and 6 months after placement of a paclitaxel-eluting stent (Grade B).

Intravenous antiplatelet agents

GP IIb-IIIa Inhibitors

- For all patients undergoing PCI, particularly those undergoing primary PCI, or those with refractory UA or other high-risk features, use of a GP IIb-IIIa antagonist (abciximab or eptifibatide) [Grade A] is recommended.

In patients undergoing PCI for STEMI, abciximab over eptifibatide (Grade A) is recommended.
Remark: Whenever possible, abciximab should be started prior to balloon inflation.

- Administration of abciximab as a 0.25 mg/kg bolus followed by a 12-h infusion at a rate of 10 micg/min (Grade A) and eptifibatide as a double bolus (each of 180 micg/kg administered 10 min apart), followed by an 18-h infusion of 2.0 micg/kg/min (Grade A) is recommended.

- In patients undergoing PCI, the use of tirofiban as an alternative to abciximab (Grade A) is not recommended.

- For patients with NSTEMI/UA who are designated as moderate-to-high risk based on TIMI score, it is recommended that upstream use of a GP IIb-IIIa antagonist (either eptifibatide or tirofiban) be started as soon as possible prior to PCI (Grade A).

- In NSTEMI/UA patients who receive upstream treatment with tirofiban, it is recommended that PCI be deferred for at least 4 h after initiating the tirofiban infusion (Grade C).

- With planned PCI in NSTEMI/UA patients with an elevated troponin level, it is recommended that abciximab be started within 24 h prior to the intervention (Grade A).

Heparins

Unfractionated Heparin

- In patients receiving a GP IIb-IIIa inhibitor, a heparin bolus of 50 to 70 IU/kg to achieve a target ACT >200 s (Grade B) is recommended.

- In patients not receiving a GP IIb-IIIa inhibitor, it is recommended that heparin be administered in doses sufficient to produce an ACT of 250 to 350 s (Grade A).

- A weight-adjusted heparin bolus of 60 to 100 IU/kg (Grade C) is recommended.

- In patients after uncomplicated PCI, routine postprocedural infusion of heparin (Grade A) is not recommended.

Low Molecular Weight Heparin

- In patients who have received LMWH prior to PCI, it is recommended that administration of additional anticoagulant therapy should depend on the timing of the last dose of LMWH (Grade B)

. If the last dose of enoxaparin was administered <8 h prior to PCI, no additional anticoagulant therapy (Grade C) should be given
. If the last dose of enoxaparin was administered between 8 h and 12 h before PCI, a 0.3 mg/kg bolus of IV enoxaparin at the time of PCI (Grade C) is recommended
. If the last enoxaparin dose was administered >12 h before PCI, conventional anticoagulation therapy can be used. during PCI(Grade C)

Vitamin K Antagonists

- In patients who undergo PCI with no other indication for systemic anticoagulation therapy, routine use of warfarin (or other vitamin K antagonists) after PCI (Grade A) is not recommended.

Ischaemic stroke

1. Acute Ischemic Stroke (AIS):

Thrombolytic Therapy in Acute Stroke

IV tPA for AIS within 3 h of symptom onset

- For eligible patients, it is recommended that IV tPA in a dose of 0.9 mg/kg (maximum of 90 mg) is administered, with 10% of the total dose administered as an initial bolus, and the remainder infused over 60 min, provided that treatment is initiated within 3 h of clearly defined symptom onset (Grade A).

- For patients with extensive (more than one third of the MCA territory) and clearly identifiable hypodensity on CT, thrombolytic therapy (Grade A) is not recommended.

IV tPA for AIS between 3 h to 6 h of symptom onset

- For unselected patients with AIS of >3 h but <6 h, clinicians should **not** use IV tPA (Grade B).

Intra-arterial thrombolysis for AIS

- For patients with angiographically demonstrated MCA occlusion and no signs of major early infarction on the baseline CT scan, who can be treated within 6 h of symptom onset, intra-arterial thrombolytic therapy with tPA can be used (Grade C).

- For patients with acute basilar artery thrombosis and without major CT/MRI evidence of infarction, intra-arterial thrombolysis with tPA can be used (Grade C).

AIS: Patients Not Eligible for Thrombolysis or Thrombolysis not available

Anticoagulants for altering outcomes among acute stroke in patients not eligible for thrombolysis

- For patients with AIS, clinicians should not use full-dose anticoagulation with IV, subcutaneous, or low molecular weight heparins or heparinoids (Grade C).

Antiplatelet agents for altering outcomes in acute stroke in patients not eligible for thrombolysis

- For patients with ischemic stroke who are not receiving thrombolysis, early aspirin therapy, 150 to 300 mg/d is recommended (Grade A).

Antithrombotic therapy for prevention of DVT and PE in AIS

- For acute stroke patients with restricted mobility, prophylactic low-dose subcutaneous heparin or low molecular weight heparins or heparinoids is recommended. (Grade A)

- For patients who have contraindications to anticoagulants, we recommend use of intermittent pneumatic compression devices or elastic stockings (Grade B).

DVT/PE Prophylaxis in Patients with Intracerebral Hematoma (ICH)
Heparin for DVT/PE prophylaxis in patients with ICH

- In patients with an acute ICH, the initial use intermittent pneumatic compression (Grade 1C) is recommended. In stable patients, low-dose subcutaneous heparin may be initiated as soon as the second day after the onset of the hemorrhage (Grade C).

2. Stroke Prevention

Prevention of cerebral ischemic events in patients with noncardioembolic TIA or stroke: antiplatelet drugs vs placebo or vs an alternative antiplatelet drug

- In patients who have experienced a noncardioembolic stroke or TIA (ie, atherothrombotic, lacunar, or cryptogenic), treatment with an antiplatelet agent is recommended (Grade A). Aspirin at a dose of 75 to 300 mg qd; the combination of aspirin, 25 mg, and extended release dipyridamole, 200 mg bid; or clopidogrel, 75 mg qd, are all acceptable options for initial therapy.

- In patients receiving aspirin who are at moderateto-high risk of bleeding complications, use of low doses of aspirin, 50 to 100 mg/d is recommended (Grade A).

- In patients who have experienced a noncardioembolic stroke or TIA, use of the combination of aspirin and extended-release dipyridamole, 25/200 mg bid, over aspirin (Grade B), and clopidogrel over aspirin (Grade C) is recommended.

- For patients who are allergic to aspirin, clopidogrel is preferred.(Grade A).

Prevention of noncardioembolic cerebral ischemic events: oral anticoagulants

- For most patients with noncardioembolic stroke or TIA, it is recommended that antiplatelet agents are used over oral anticoagulants (Grade A).

- For patients with well-documented prothrombotic disorders, oral anticoagulants over antiplatelet agents (Grade C) is recommended.

Prevention of cerebral ischemic events in patients undergoing carotid endarterectomy: antiplatelet agents

- In patients undergoing carotid endarterectomy, aspirin 75 to 300 mg/d, prior to and following the procedure is recommended (Grade A).

Prevention of cardioembolic cerebral ischemic events

Patients with stroke with underlying atrial fibrillation: anticoagulation

- In patients with atrial fibrillation who have had a recent stroke or TIA, long-term oral anticoagulation (target INR, 2.5; range, 2.0 to 3.0) is recommended [Grade A].

Patients with stroke with underlying atrial fibrillation: antiplatelet agents

- Aspirin is recommended for patients with cardioembolic stroke who have contraindications to anticoagulant therapy (Grade A).

Patients with aortic atheromata

- In patients with stroke associated with aortic atherosclerotic lesions, it is recommended that antiplatelet therapy be used over no therapy (Grade B). For patients with cryptogenic stroke associated with mobile aortic arch thrombi, either oral anticoagulants or antiplatelet agents can be used (Grade C).

Patients with patent foramen ovale (PFO)

- In patients with cryptogenic ischemic stroke and a PFO, it is recommended that antiplatelet therapy be used over no therapy Grade A), and antiplatelet agents over anticoagulation (Grade B).

Mitral valve strands and prolapse

- In patients with mitral valve strands or prolapse, who have a history of TIA or stroke, antiplatelet therapy is recommended (Grade A).

Cerebral Venous Sinus Thrombosis

Anticoagulation for cerebral venous sinus thrombosis

- In patients with venous sinus thrombosis, it is recommended that clinicians use full dose unfractionated heparin (Grade A) or low molecular weight heparin (Grade A) over no anticoagulant therapy during the acute phase, even in the presence of hemorrhagic infarction. In these patients, oral anticoagulation for 3 to 6 months (target INR, 2.5; range, 2.0 to 3.0) is recommended [Grade B].

Atrial fibrillation

Efficacy of Long-term Antithrombotic Therapy in AF

For patients with any high-risk factor or more than one moderate-risk factor, warfarin (target INR 2.5; range, 2.0 to 3.0) is recommended. See under "Antithrombotic Therapy in Patients With Mechanical and Biological Prosthetic Heart Valves" for target INRs in patients with mechanical heart valves. For patients with one moderate-risk factor, aspirin, 300 mg/d, or warfarin (target INR 2.5; range, 2.0 to 3.0) is recommended. For patients with no high-risk factors and no moderate-risk factors, aspirin, 325 mg/d is recommended.

Risk Stratification

High-risk factors include prior stroke/TIA or systemic embolus, history of hypertension, poor LV systolic function, age >75 years, rheumatic mitral valve disease, and prosthetic heart valve.

Moderate risk factors (factors for stroke that have been identified in AF patients in various studies but are not as strong or consistent as the high-risk factors listed above) include age 65 to 75 years, diabetes mellitus, and coronary artery disease with preserved LV systolic function.

High-Risk Patients

- Use of adjusted-dose warfarin anticoagulation (target INR 2.5; range 2.0 to 3.0) rather than aspirin is recommended in patients with AF at high risk for ischemic stroke because it markedly decreases the risk of ischemic stroke in patients with AF (grade A).

- For high-risk patients, aspirin therapy is recommended if adjusted-dose warfarin is contraindicated or declined by the patient and if there are no contraindications to aspirin (grade A).

- In AF patients with rheumatic mitral valve disease or prosthetic heart valves (mechanical or tissue valves), Oral Anti Coagulant (OAC) is recommended (grade A).

Low-Risk Patients

- Patients with AF who are <65 years with no clinical or echocardiographic evidence of cardiovascular disease should be treated with aspirin (grade C).

Moderate-Risk Patients

- Some AF patients will have a risk of stroke that is between that of the high-risk and low-risk groups mentioned. For these patients, the difference between warfarin vs aspirin with regard to the absolute stroke risk is likely to be small. Use of either or aspirin for patients with one of these moderate risk factors is appropriate (grade A in comparison to no treatment).
- Patients with more than one of these moderate-risk factors are at higher risk of stroke than are those with only one risk factor, and these patients should be treated in the same manner as high-risk patients (see above; grade C).

The ultimate choice of therapy depends on many factors, including the clinician's assessment of the magnitude of the patient's risk (eg, whether the patient has single or multiple risk factors), the ability to provide high-quality monitoring of the intensity of OAC, the patient's risk of bleeding with OAC, and patient preference.

Anticoagulation for Elective Cardioversion

AF

- oral anticoagulant therapy is recommended (target INR 2.5; range 2.0 to 3.0) for 3 weeks before and at least 4 weeks after elective DC cardioversion of AF patients (grade A).

- Alternatively, AF patients can undergo anticoagulation then undergo TEE, and have cardioversion performed without delay if no thrombi are seen (grade B). For these patients, adjusted-dose warfarin therapy should still be continued until normal sinus rhythm has been maintained for at least 4 weeks.

- Although data are limited, the risk of embolism following cardioversion in patients who have been in AF for <48 h appears to be low. However, the use of anticoagulation during the pericardioversion period is recommended (grade C).

Atrial Flutter and Supraventricular Tachycardia

- OAC at the time of cardioversion in patients with atrial flutter should be managed in a manner similar to that used for AF (grade C).
- In the absence of prior thromboembolism, antithrombotic therapy is not recommended for cardioversion of supraventricular tachycardia (grade C).

Treatment of potential precipitants of AF (ie, thyrotoxicosis, pneumonia, congestive heart failure) should be completed prior to attempting elective DC cardioversion.

Valvular Heart Disease

Mitral Valve Disease

Rheumatic Mitral Valve Disease With AF or a History of Systemic Embolism

For patients with rheumatic mitral valve disease and AF, or a history of previous systemic embolism:

- Long-term oral anticoagulant therapy (target INR, 2.5; range, 2.0 to 3.0) is recommended [Grade A].
- Clinicians should not use concomitant therapy with OAC and Aspirin in these patients (Grade C).

Underlying values and preferences: This recommendation places a relatively high value on avoiding the additional bleeding risk associated with concomitant OAC and antiplatelet therapy.

For patients with rheumatic mitral valve disease with AF or a history of systemic embolism who suffer systemic embolism while receiving OACs at a therapeutic INR:

- Adding aspirin, 75 to 100 mg/d is recommended (Grade B). For those patients unable to take aspirin, dipyridamole, 400 mg/d, or clopidogrel 75 mg can be given instead (Grade B).

Patients With Mitral Valve Disease in Sinus Rhythm

- In patients with rheumatic mitral valve disease and normal sinus rhythm with a left atrial diameter > 5.5 cm, long-term OAC (target INR, 2.5; range, 2.0 to 3.0) is recommended [Grade C].
- In patients with rheumatic mitral valve disease and normal sinus rhythm with a left atrial diameter <5.5cm, we suggest clinicians not use antithrombotic therapy (Grade C).

Patients Undergoing Mitral Valvuloplasty

- For patients undergoing mitral valvuloplasty, we suggest anticoagulation with vitamin K antagonists with a target INR of 2.5 (range, 2.0 and 3.0) for 3 weeks prior to the procedure and for 4 weeks after the procedure (Grade C).

Mitral Valve Prolapse (MVP)

- In people with MVP who have not experienced systemic embolism, unexplained TIAs, or AF, antithrombotic therapy is not recommended (Grade B).

- In patients with MVP who have documented but unexplained TIAs, long-term aspirin therapy, 50 to 150 mg/d is recommended (Grade A).

- In patients with MVP who have documented systemic embolism or recurrent TIAs despite aspirin therapy, long-term vitamin K antagonist therapy (target INR, 2.5; range, 2.0 to 3.0) should be used. [Grade C].

Mitral annular calcification (MAC)

- In patients with MAC complicated by systemic embolism, not documented to be calcific embolism, treatment with long-term OAC therapy (target INR, 2.5; INR range, 2.0 to 3.0) should be considered [Grade C].

Aortic Valve and Aortic Arch Disorders

- In patients with aortic valve disease, clinicians should not use long-term vitamin K antagonist therapy unless they have another indication for anticoagulation (Grade C).

- OAC therapy should be considerd in patients with mobile aortic atheromas and aortic plaques >4 mm as measured by Trans esophageal echocardiography (TEE) (Grade C).

Prosthetic Heart Valves

Mechanical Prosthetic Heart Valves

- Vitamin K antagonists are recommended for all patients with mechanical prosthetic heart valves, (Grade A). Unfractionated heparin or LMWH should be administered until the INR is stable and at a therapeutic level for 2 consecutive days (Grade C).

- For patients with a St. Jude Medical bileaflet valve in the aortic position, a target INR of 2.5 (range 2.0 to 3.0) is recommended [Grade A].

- For patients with tilting disk valves and bileaflet mechanical valves in the mitral position, we recommend a target INR of 3.0 (range 2.5 to 3.5) [Grade A].

- For patients with CarboMedics bileaflet valve or Medtronic Hall tilting disk mechanical valves in the aortic position, normal left atrium size, and sinus rhythm, a target INR of 2.5 (range, 2.0 to 3.0) is recommended [Grade A].

- In patients who have mechanical valves and additional risk factors such as AF, myocardial infarction, left atrial enlargement, endocardial damage, and low ejection fraction, a target INR of 3.0 (range 2.5 to 3.5), combined with low doses of aspirin, 75 to 100 mg/d is recommended (Grade A).

- For patients with caged ball or caged disk valves, a target INR of 3.0 (range, 2.5 to 3.5) should be maintained in combination with aspirin, 75 to 100 mg/d (Grade B).

- For patients with mechanical prosthetic heart valves who suffer systemic embolism despite a therapeutic INR, aspirin 75 to 100 mg/d, is recommended in addition to vitamin K antagonists. The INR should be maintained at a target of 3.0 (range 2.5 to 3.5) [Grade A].

- In patients with prosthetic heart valves in whom vitamin K antagonist must be discontinued, LMWH (Grade B) or aspirin 75–100 mg/day is recommended (Grade 1C).

Prosthetic Heart Valves

Bioprosthetic Valves

First 3 months after valve insertion

- For patients with bioprosthetic valves in the mitral position, vitamin K antagonists with a target INR of 2.5 (range 2.0 to 3.0) is recommended for the first 3 months after valve insertion (Grade A) or patients with bioprosthetic valves in the aortic position, vitamin K antagonists can be given with a target INR of 2.5 (range 2.0 to 3.0) for the first 3 months after valve insertion (Grade C) or aspirin 80–100 mg/day (Grade B).

- In patients who have undergone valve replacement, heparin (low molecular weight or unfractionated) should be given until the INR is stable at therapeutic levels for 2 consecutive days (Grade C).

- For patients with bioprosthetic valves who have a history of systemic embolism, vitamin K antagonists for 3 to 12 months is recommended (Grade B).

- In patients with bioprosthetic valves who have evidence of a left atrial thrombus at surgery, vitamin K antagonists with a dose sufficient to prolong the INR to a target of 2.5 (range 2.0 to 3.0)is recommended[Grade B].

Values and preferences: This recommendation places a relatively high value on preventing thromboembolic events and a relatively lower value on bleeding complications.

Long-term Treatment

- In patients with bioprosthetic valves who have AF, long-term treatment with vitamin K antagonists with a target INR of 2.5 (range 2.0 to 3.0) is recommended [Grade A].

- For patients with bioprosthetic valves who are in sinus rhythm and do not have AF, longterm therapy with aspirin, 75 to 100 mg/d is recommended (Grade A).

Infective Endocarditis and Nonbacterial Thrombotic Endocarditis

- In patients with a mechanical prosthetic valve and endocarditis who have no contraindications, vitamin K antagonists should be continued long term (Grade C).

- For patients with NBTE and systemic or pulmonary emboli, treatment with full-dose unfractionated IV or subcutaneous heparin is recommended (Grade B).

- For patients with disseminated cancer or debilitating disease with aseptic vegetations, full-dose unfractionated heparin should be administered (Grade C).

Prevention of Venous Thromboembolism

General Recommendations

- It is recommended that mechanical methods of prophylaxis be used primarily in patients who are at high risk of bleeding (Grade A) or as an adjunct to anticoagulant-based prophylaxis (Grade B). Careful attention should be directed toward ensuring the proper use of, and optimal compliance with, the mechanical device (Grade A).

- The use of aspirin alone as prophylaxis against VTE for any patient group is not recommended. (Grade A)

- For each of the antithrombotic agents, it is recommended that clinicians consider the manufacturer's suggested dosing guidelines (Grade B).

- Consideration of renal impairment is important when deciding on doses of LMWH, fondaparinux, the direct thrombin inhibitors, and other antithrombotic drugs that are cleared by the kidneys, particularly in elderly patients and those who are at high risk for bleeding (Grade B)

- In all patients undergoing neuraxial anesthesia or analgesia, it is recommended to exercise special caution when using anticoagulant prophylaxis (Grade A).

General, Vascular, Gynecologic, and Urologic Surgery

General surgery

- In low-risk general surgery patients (Table 5) who are undergoing a minor procedure, are <40 years of age, and have no additional risk factors, the use of specific prophylaxis other than early and persistent mobilization is not recommended (Grade A).

- Moderate-risk general surgery patients are those patients undergoing a nonmajor procedure and are between the ages of 40 and 60 years or have additional risk factors, or those patients who are undergoing major operations and are <40 years of age with no additional risk factors. In these patients prophylaxis with LDUH, 5,000 U bid, or LMWH, <3,400 U once daily is recommended (both Grade A).

- Higher-risk general surgery patients are those undergoing nonmajor surgery and are <60 years of age or have additional risk factors, or patients undergoing major surgery who are <40 years of age or have additional risk factors. Thromboprophylaxis with LDUH, 5,000 U tid, or LMWH, <3,400 U daily is recommended (both Grade A).

- In high-risk general surgery patients with multiple risk factors, pharmacologic methods (ie, LDUH, tid, or LMWH, < 3,400 U daily) combined with the use of GCS and/or IPC is recommended (Grade A).

- In general surgery patients with a high risk of bleeding, the use of mechanical prophylaxis with properly fitted GCS or IPC, at least initially until the bleeding risk decreases is recommended (Grade A).

- In selected high-risk general surgery patients, including those who have undergone major cancer surgery, post-hospital discharge prophylaxis with LMWH should be considered (Grade B).

Vascular surgery

- In patients undergoing vascular surgery who do not have additional thromboembolic risk factors, clinicians should not routinely use thromboprophylaxis (Grade C).
- For patients undergoing major vascular surgical procedures who have additional thromboembolic risk factors, prophylaxis with LDUH or LMWH is recommended (Grade A).

Gynecologic surgery

- For gynecologic surgery patients undergoing brief procedures of <30 min for benign disease, the use of specific prophylaxis other than early and persistent mobilization is not recommended (Grade A).

- For patients undergoing laparoscopic gynecologic procedures, in whom additional VTE risk factors are present, the use of thromboprophylaxis with one or more of the following: LDUH, LMWH, IPC, or GCS is recommended (all Grade B).

- It is recommended that thromboprophylaxis be used in all major gynecologic surgery patients (Grade A).

- For patients undergoing major gynecologic surgery for benign disease, without additional risk factors, d LDUH, 5,000 U bid is recommended (Grade A). Alternatives include once-daily prophylaxis with LMWH 3,400 U/d (Grade A), or IPC started just before surgery and used continuously while the patient is not ambulating (Grade A).

- For patients undergoing extensive surgery for malignancy, and for patients with additional VTE risk factors, routine prophylaxis with LDUH, 5,000 U tid (Grade A), or higher doses of LMWH (ie,3,400 U/d) is recommended [Grade A]. Alternative considerations include IPC alone continued until hospital discharge (Grade A), or a combination of LDUH or LMWH plus mechanical prophylaxis with GCS or IPC (all Grade B).

- For patients undergoing major gynecologic procedures, consider continued prophylaxis until discharge from the hospital (Grade B). For patients who are at particularly high risk, including those who have undergone cancer surgery and who are >60 years of age or have previously experienced a VTE, consider continuing prophylaxis for 2 to 4 weeks after hospital discharge (Grade C).

Urologic surgery

- In patients undergoing transurethral or other low-risk urologic procedures, the use of specific prophylaxis other than early and persistent mobilization is not recommended (Grade A).

- For patients undergoing major, open urologic procedures, routine prophylaxis with LDUH twice daily or three times daily is recommended (Grade A). Acceptable alternatives include prophylaxis with IPC and/or GCS (Grade A) or LMWH (Grade A).

- For urologic surgery patients who are actively bleeding or are at very high risk for bleeding, the use of mechanical prophylaxis with GCS and/or IPC at least until the bleeding risk decreases is recommended (Grade A).

- For patients with multiple risk factors, combining GCS and/or IPC with LDUH or LMWH is recommended (Grade A).

Laparoscopic surgery

- Routine thromboprophylaxis in these patients, other than aggressive mobilization is not recommended (Grade A).

- For patients undergoing laparoscopic procedures and who have additional thromboembolic risk factors, the use of thromboprophylaxis with one or more of the following: LDUH, LMWH, IPC, or GCS is recommended (Grade A).

Orthopedic Surgery

Elective hip arthroplasty

- For patients undergoing elective THR the routine use of one of the following 2 anticoagulants is recommended: (1) LMWH (at a usual high-risk dose, started 12 h before surgery or 12 to 24 h after surgery, or 4 to 6 h after surgery at half the usual high-risk dose and then increasing to the usual high-risk dose the following day or (2) adjusted-dose VKA started preoperatively or the evening after surgery (INR target, 2.5; INR range, 2.0 to 3.0) [all Grade A].

- The use of aspirin, dextran, LDUH, GCS, IPC, or VFP as the only method of thromboprophylaxis in these patients is not recommended (Grade A).

Elective knee arthroplasty

- For patients undergoing elective TKA, routine thromboprophylaxis using LMWH (at the usual high-risk dose) or adjusted-dose VKA (target INR, 2.5; INR range, 2.0 to 3.0) is recommended [all Grade A].

- The optimal use of IPC is an alternative option to anticoagulant prophylaxis (Grade A).

- The use of any of the following as sole methods of thromboprophylaxis: aspirin (Grade A); LDUH (Grade A); or VFP is not recommended (Grade A).

Knee arthroscopy

- Routine use of thromboprophylaxis in these patients, other than early mobilization is not recommended (Grade C).

- For patients undergoing arthroscopic knee surgery who are at a higher than usual risk, based on preexisting VTE risk factors or following a prolonged or complicated procedure, thromboprophylaxis with LMWH should be considered (Grade C).

Hip fracture surgery (HFS)

- For patients undergoing HFS, the routine use of LMWH at the usual high-risk dose (Grade A), adjusted-dose VKA (target INR, 2.5; INR range, 2.0 to 3.0) is recommended [Grade C], or LDUH (Grade A).

- The use of aspirin alone is not recommended (Grade A).
- If surgery is likely to be delayed, it is recommended that prophylaxis with either LDUH or LMWH be initiated during the time between hospital admission and surgery (Grade A).

- Mechanical prophylaxis is recommended if anticoagulant prophylaxis is contraindicated because of a high risk of bleeding (Grade A).

Other prophylaxis issues in major orthopedic surgery

- For major orthopedic surgical procedures, it is recommended that a decision about the timing of the initiation of pharmacologic prophylaxis be based on the efficacy-to-bleeding tradeoffs for that particular agent (Grade A). For LMWH, there are only small differences between starting preoperatively or postoperatively, and both options are acceptable (Grade A).

- The routine use of Duplex Ultra Sound screening at the time of hospital discharge in asymptomatic patients following major orthopedic surgery is not recommended (Grade A).

- It is recommended that patients undergoing THR, TKA, or HFS receive thromboprophylaxis with LMWH (using a high-risk dose) or a VKA (target INR, 2.5; INR range, 2.0 to 3.0) for at least 10 days (Grade A).

- It is recommended that patients undergoing THR or HFS be given extended prophylaxis for up to 28 to 35 days after surgery (Grade A). The recommended options for THR include LMWH (Grade A), or VKA (Grade A). The recommended options following HFS are LMWH (Grade A) or a VKA (Grade A).

Elective spine surgery

- For spinal surgery patients with no additional risk factors, the routine use of any thromboprophylaxis modality, apart from early and persistent mobilization is not recommended (Grade B).
- It is recommended that some form of prophylaxis be used in patients undergoing spinal surgery who exhibit additional risk factors such as advanced age, known malignancy, presence of a neurologic deficit, previous VTE, or an anterior surgical approach (Grade A).
- For patients with additional risk factors, any of the following prophylaxis options is recommended: postoperative LDUH alone (Grade A); postoperative LMWH alone (Grade A); or perioperative IPC alone (Grade A). Other considerations include perioperative GCS alone (Grade C), or perioperative IPC combined with GCS (Grade C). In patients with multiple risk factors for VTE, combining LDUH or LMWH with GCS and/or IPC is recommended (Grade A).

Isolated lower extremity injuries

- Clinicians should not use thromboprophylaxis routinely in patients with isolated lower extremity injuries (Grade B).

Neurosurgery

- It is recommended that thromboprophylaxis be routinely used in patients undergoing major neurosurgery (Grade A).
- The use of IPC with or without GCS in patients undergoing intracranial neurosurgery is recommended (Grade A).

- Acceptable alternatives to the above options are prophylaxis with LDUH (Grade 2B) or postoperative LMWH (Grade C).

- The combination of mechanical prophylaxis (ie, GCS and/or IPC) and pharmacologic prophylaxis (ie, LDUH or LMWH) in high-risk neurosurgery patients is recommended (Grade C).

Trauma, Spinal Cord Injury, Burns

Trauma

- It is recommended that all trauma patients with at least one risk factor for VTE receive thromboprophylaxis, if possible (Grade A).
- In the absence of a major contraindication, it is recommended that clinicians use LMWH prophylaxis starting as soon as it is considered safe to do so (Grade A).
- It is recommended that mechanical prophylaxis with IPC, or possibly with GCS alone, be used if LMWH prophylaxis is delayed or if it is currently contraindicated due to active bleeding or a high risk for hemorrhage (Grade A).
- DUS screening in patients who are at high risk for VTE (eg, the presence of a SCI, lower extremity or pelvic fracture, major head injury, or an indwelling femoral venous line), and who have received suboptimal prophylaxis or no prophylaxis is recommended (Grade B).
- The use of Inferior Vena Caval Filters as primary prophylaxis in trauma patients is not recommended (Grade B).
- The continuation of thromboprophylaxis until hospital discharge, including the period of inpatient rehabilitation is recommended (Grade A). Consider continuing prophylaxis after hospital discharge with LMWH or a VKA (target INR, 2.5; INR range, 2.0 to 3.0) in patients with major impaired mobility (Grade C).

Acute spinal cord injury (SCI)

- It is recommended that thromboprophylaxis be provided for all patients with acute SCIs (Grade A).
- The use of LDUH, GCS, or IPC as single prophylaxis modalities (Grade A) is not recommended.
- In patients with acute SCI, prophylaxis with LMWH, to be commenced once primary hemostasis is evident is recommended (Grade A). The combined use of IPC and either LDUH (Grade C) or LWMH (Grade C) as alternatives to LMWH should be considered.
- The use of IPC and/or GCS when anticoagulant prophylaxis is contraindicated early after injury is recommended (Grade A).
- The use of an IVCF as primary prophylaxis against PE is not recommended (Grade B).
- During the rehabilitation phase following acute SCI, the continuation of LMWH prophylaxis or conversion to an oral VKA (INR target, 2.5; INR range, 2.0 to 3.0) is recommended [Grade B].

Burns

- It is recommended that burn patients with additional risk factors for VTE, including one or more of the following: advanced age, morbid obesity, extensive or lower extremity burns, concomitant lower extremity trauma, use of a femoral venous catheter, and/or prolonged immobility, receive thromboprophylaxis, if possible (Grade A).
- If there are no contraindications, the use of either LDUH or LMWH, starting as soon as it is considered safe to do so is recommended (Grade A).

Medical conditions

- In acutely ill medical patients who have been admitted to the hospital with congestive heart failure or severe respiratory disease, or who are confined to bed and have one or more additional risk factors, including active cancer, previous VTE, sepsis, acute neurologic disease, or inflammatory bowel disease, prophylaxis with LDUH (Grade A) or LMWH is recommended (Grade A).

- In medical patients with risk factors for VTE, and in whom there is a contraindication to anticoagulant prophylaxis, the use of mechanical prophylaxis with GCS or IPC is recommended (Grade A).

Cancer patients

- It is recommended that cancer patients undergoing surgical procedures receive prophylaxis that is appropriate for their current risk state (Grade A). Refer to the recommendations in the relevant surgical subsections.

- It is recommended that hospitalized cancer patients who are bedridden with an acute medical illness receive prophylaxis that is appropriate for their current risk state (Grade A). Refer to the recommendations in the section dealing with medical patients.

- Clinicians should not routinely use prophylaxis to try to prevent thrombosis related to longterm indwelling Central Venous Catheters in cancer patients (Grade C). Specifically, we suggest that clinicians not use LMWH (Grade C), and the use of fixed-dose warfarin is recommended against (Grade A) for this indication.

Critical care

- It is recommended that, on admission to a critical care unit, all patients be assessed for their risk of VTE. Accordingly, most patients should receive thromboprophylaxis (Grade A).

- For patients who are at high risk for bleeding, mechanical prophylaxis with GCS and/or IPC until the bleeding risk decreases is recommended (Grade A).

- For ICU patients who are at moderate risk for VTE (eg, medically ill or postoperative patients), using LDUH or LMWH prophylaxis is recommended (Grade A).

- For patients who are at higher risk, such as that following major trauma or orthopedic surgery, LMWH prophylaxis is recommended (Grade A).

Long distance travel

- The following general measures are recommended for long-distance travelers (ie, flights of >6 h duration): avoidance of constrictive clothing around the lower extremities or waist; avoidance of dehydration; and frequent calf muscle stretching (Grade B).

- For long-distance travelers with additional risk factors for VTE, the general strategies listed above are recommended. If active prophylaxis is considered, because of the perceived increased risk of venous thrombosis, the use of properly fitted, below-knee GCS providing 15 to 30 mm Hg of pressure at the ankle (Grade C), or a single prophylactic dose of LMWH injected prior to departure (Grade C) should be considered .

- The use of aspirin for VTE prevention associated with travel is not recommended (Grade A).

Treatment of Deep Venous Thrombosis

Initial treatment of acute DVT of the leg

- For patients with objectively confirmed DVT, short-term treatment with SC LMWH or IV UFH or SC UFH is recommended (all Grade A).

- For patients with a high clinical suspicion of DVT, treatment with anticoagulants while awaiting the outcome of diagnostic tests is recommended (Grade A).

- In acute DVT, initial treatment with LMWH or UFH for at least 5 days is recommended (Grade B).

- Initiation of VKA together with LMWH or UFH on the first treatment day and discontinuation of heparin when the INR is stable and >2.0 for 2 consecutive days is recommended (Grade A).

IV unfractionated heparin for the initial treatment of DVT

- If IV UFH is chosen, it is recommended that it be administered by continuous infusion with dose adjustment to achieve and maintain an aPTT prolongation of 1.5-2.5 (Grade A).

Subcutaneous unfractionated heparin for the initial treatment of DVT

- In patients with acute DVT, it is recommended that SC administered UFH can be used as an adequate alternative to IV UFH (Grade A).

- For patients who receive SC UFH, an initial dose of 35,000 U/24 h SC is recommended, with subsequent dosing to maintain the aPTT in the therapeutic range (Grade A).

Low-molecular-weight heparin for the initial treatment of DVT

- In patients with acute DVT, initial treatment with LMWH SC once or twice daily over UFH as an outpatient if possible (Grade B), and as inpatient if necessary is recommended(Grade A).

- In patients with severe renal failure, IV UFH over LMWH is recommended (Grade C).

Systematically administered thrombolysis in the initial treatment of DVT

- In patients with DVT, the routine use of IV thrombolytic treatment is not recommended (Grade A).

- In selected patients, such as those with massive ileofemoral DVT at risk of limb gangrene secondary to venous occlusion, IV thrombolysis should be considered (Grade C).

Catheter-directed thrombolysis in the initial treatment of DVT

- In patients with DVT, the routine use of catheter-directed thrombolysis is not recommended (Grade B).

- It is suggested that this treatment should be confined to selected patients such as those requiring limb salvage (Grade2C).

Catheter extraction or fragmentation and surgical thrombectomy for the initial treatment of DVT

- In patients with DVT, the routine use of venous thrombectomy is not recommended (Grade B).

- In selected patients such as patients with massive ileofemoral DVT at risk of limb gangrene secondary to venous occlusion, venous thrombectomy should be considered (Grade C).

Vena caval interruption for the initial treatment of DVT

- For most patients with DVT, the routine use of a vena cava filter in addition to anticoagulants is not recommended (Grade A).
- The placement of an inferior vena caval filter should be considered in patients with a contraindication for, or a complication of anticoagulant treatment (Grade C), as well as in those with recurrent thromboembolism despite adequate anticoagulation (Grade C).

Immobilization

- For patients with DVT, ambulation as tolerated is recommended (Grade A).

Long-term Treatment of Acute DVT of the Leg

Vitamin K antagonists for the long-term treatment of DVT

- For patients with a first episode of DVT secondary to a transient (reversible) risk factor, long-term treatment with a VKA for 3 months over treatment for shorter periods is recommended (Grade A).
- For patients with a first episode of idiopathic DVT, treatment with a VKA at least 6 to 12 months is recommended (Grade A).
- It is recommended that patients with first-episode of idiopathic DVT be considered for indefinite anticoagulant therapy (Grade C).
- For patients with DVT and cancer, LMWH for the first 3 to 6 months of long-term anticoagulant therapy is recommended (Grade A). For these patients, anticoagulant therapy is recommended indefinitely or until the cancer is resolved (Grade B).

- For patients with a first episode of DVT who have documented antiphospholipid antibodies or who have two or more thrombophilic conditions (eg, combined factor V Leiden and prothrombin 20210 gene mutations), treatment for 12 months is recommended (Grade A). Indefinite anticoagulant therapy should be considered in these patients (Grade C).

- For patients with a first episode of DVT who have documented deficiency of antithrombin, deficiency of protein C or protein S, or the factor V Leiden or prothrombin 20210 gene mutation, homocysteinemia, or high factor VIII levels (>90th percentile of normal), treatment for 6 to 12 months is recommended(Grade A). Indefinite therapy should be considered as for patients with idiopathic thrombosis (Grade C).

- For patients with two or more episodes of objectively documented DVT, indefinite treatment should be considered (Grade B).

- We recommend that the dose of VKA be adjusted to maintain a target INR of 2.5 (range, 2.0 and 3.0) for all treatment durations (Grade A). High-intensity VKA therapy (INR range, 3.1 to 4.0) [Grade 1A] is not recommended. Low-intensity therapy (INR range, 1.5 to 1.9) compared to INR range of 2.0 to 3.0 is also not recommended (Grade A).

- In patients who receive indefinite anticoagulant treatment, the risk-benefit of continuing such treatment should be reassessed in the individual patient at periodic intervals (Grade B).

- Repeat testing with compression ultrasonography for the presence or absence of residual thrombosis or measurement of plasma D-dimer is recommended (Grade C).

Low-molecular-weight heparin for the longterm treatment of DVT

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

Remark: The regimens of LMWH that have been established to be effective for long-term treatment in randomized trials are dalteparin, 200 IU/kg body weight qd for 1 month, followed by 150 IU/kg qd thereafter, or tinzaparin at 175 IU/kg body weight SC qd.

The Post-Thrombotic Syndrome

Elastic stockings for the prevention of the post-thrombotic syndrome

- The use of an elastic compression stocking with a pressure of 30 to 40 mm Hg at the ankle during first 2 years after an episode of DVT is recommended (Grade A).

Physical treatment of the post-thrombotic syndrome

- A course of intermittent pneumatic compression is recommended for patients with severe edema of the leg due to PTS (Grade C).
- The use of elastic compression stockings is recommended for patients with mild edema of the leg due to the PTS (Grade C).

Initial Treatment of Acute Pulmonary Embolism

IV unfractionated heparin or low-molecularweight heparin for the initial treatment of pulmonary embolism

- For patients with objectively confirmed nonmassive PE, short-term treatment with SC LMWH, or IV UFH is recommended (both Grade A).
- For patients with a high clinical suspicion of PE, treatment with anticoagulants while awaiting the outcome of diagnostic tests is recommended (Grade A).
- In patients with acute nonmassive PE, LMWH over UFH is recommended (Grade A).
- In acute nonmassive PE, initial treatment with LMWH or UFH for at least 5 days is recommended (Grade B).
- In patients with acute nonmassive PE treated with LMWH, routine monitoring with anti-factor Xa levels is not recommended (Grade A).
- In patients with severe renal failure, IV UFH over LMWH is recommended (Grade C).
- If IV UFH is chosen, administration by continuous infusion with dose adjustment to achieve and maintain an aPTT prolongation corresponding to plasma heparin levels from 0.3 to 0.7 IU/mL anti-Xa activity is recommended (Grade A).
- In patients requiring large daily doses of UFH without achieving a therapeutic aPTT, the measurement of the anti-Xa level for dose guidance is recommended (Grade A).
- Initiation of VKA together with LMWH or UFH on the first treatment day and discontinuation of heparin when the INR is stable and >2.0 for 2 consecutive days is recommended (Grade A).

Systemically and locally administered thrombolytic drugs for the initial treatment of pulmonary embolism

- For most patients with PE, clinicians should not use systemic thrombolytic therapy (Grade A). In selected patients, systemic administration of thrombolytic therapy should be considered (Grade C). For patients who are hemodynamically unstable, use of thrombolytic therapy is recommended (Grade C).

- Local administration of thrombolytic therapy via a catheter is not recommended (Grade B).

- For patients with PE who receive thrombolytic regimens, use of thrombolytic regimens with a short infusion time over those with prolonged infusion times is recommended (Grade C).

Catheter extraction or fragmentation for the initial treatment of pulmonary embolism

- For most patients with PE, use of mechanical approaches (Grade B) is not recommended. In selected highly compromised patients who are unable to receive thrombolytic therapy or whose critical status does not allow sufficient time to infuse thrombolytic therapy, use of mechanical approaches should be considered (Grade C).

Pulmonary embolectemy for the initial treatment of pulmonary embolism

- For most patients with PE, pulmonary embolectomy is not recommended (Grade B). In selected highly compromised patients who are unable to receive thrombolytic therapy or whose critical status does not allow sufficient time to infuse thrombolytic therapy, pulmonary embolectomy should be considered (Grade C).

Vena caval interruption for the initial treatment of pulmonary embolism

- In PE patients with a contraindication for, or a complication of anticoagulant treatment, as well as in those with recurrent thromboembolism despite adequate anticoagulation, placement of an inferior vena caval filter is recommended (both Grade C).

Long-term Treatment of Acute Pulmonary Embolism

Vitamin K antagonists for the long-term treatment of pulmonary embolism

- For patients with a first episode of PE secondary to a transient (reversible) risk factor, long-term treatment with a VKA for at least 3 months is recommended (Grade A).
- For patients with a first episode of idiopathic PE, treatment with a VKA for at least 6 to 12 months is recommended (Grade A).
- It is recommended that patients with first-episode idiopathic PE be considered for indefinite anticoagulant therapy (Grade B).
- Underlying values and preferences. This recommendation ascribes a relatively high value to preventing recurrent thromboembolic events and a relatively low value on bleeding and cost.
- For patients with PE and cancer, it is recommended that LMWH be given for the first 3 to 6 months of long-term anticoagulant therapy (Grade A). These patients should then receive anticoagulant therapy indefinitely or until the cancer is resolved (Grade B).
- For patients with a first episode of PE who have documented antiphospholipid antibodies or who have two or more thrombophilic conditions (eg, combined factor V Leiden and prothrombin 20210 gene mutations), treatment for 12 months is recommended. (Grade B). For these patients, indefinite anticoagulant therapy should be considered (Grade C).

- For patients with a first episode of PE who have documented deficiency of antithrombin, deficiency of protein C or protein S, or the factor V Leiden or prothrombin 20210 gene mutation, homocysteinemia, or high factor VIII levels (>90th percentile of normal), treatment for 6 to 12 months is recommended (Grade A). Consider indefinite therapy for patients with idiopathic PE (Grade C)

- For patients with two or more episodes of objectively documented PE, indefinite treatment should be considered (Grade B).

- It is recommended that the dose of VKA be adjusted to maintain a target INR of 2.5 (INR range, 2.0 and 3.0) for all treatment durations (Grade A). High-intensity VKA therapy (INR range, 3.1 to 4.0) or low-intensity therapy (INR range, 1.5 to 1.9) compared to INR range of 2.0 to 3.0 (Grade A).are not recommended [Grade A].

- In patients who receive indefinite anticoagulant treatment, the risk-benefit of continuing such treatment should be reassessed in the individual patient at periodic intervals (Grade B).

LMWH for the long-term treatment of PE

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

Remark: The LMWH regimens that have been established to be effective for long-term treatment are dalteparin, 200 IU/kg body weight qd for 1 month followed by 150 IU/kg qd thereafter, and tinzaparin at 175 IU/kg body weight SC qd.

Chronic Thromboembolic Pulmonary Hypertension

Pulmonary thromboendarterectomy, vitamin K antagonists, and caval filter for the treatment of chronic thromboembolic pulmonary hypertension

- In selected patients with CTPH, ie, patients with central disease under the care of an experienced surgical/ medical team, pulmonary thromboendarterectomy is recommended (Grade B)
- It is recommended that life-long treatment with VKA to an INR of 2.0 to 3.0 be administered following pulmonary thromboendarterectomy, and also be administered to patients with CTPH who are ineligible for pulmonary thromboendarterectomy (Grade B).
- Consider the placement of a vena caval filter before or at the time of pulmonary thromboendarterectomy for CTPH (Grade C).

Superficial Thrombophlebitis

Treatment for superficial thrombophlebitis

- For patients with superficial thrombophlebitis as a complication of an infusion, topical diclofenac gel (Grade A) or oral diclofenac (Grade C) should be considered.
- For patients affected by spontaneous superficial thrombophlebitis, intermediate dosages of UFH or LMWH for at least 4 weeks (Grade C) should be considered.

Acute Upper Extremity DVT

IV unfractionated heparin or low-molecular weight heparin for the initial treatment of upper extremity DVT

- For patients with acute upper-extremity DVT, initial treatment with UFH (Grade B) or LMWH (Grade B) is recommended.

Thrombolytic therapy for the initial treatment of upper extremity DVT

- In selected patients with acute upper-extremity DVT, eg, in those with a low risk of bleeding and symptoms of recent onset, consider a short course of thrombolytic therapy for initial treatment (Grade C).

Catheter extraction, surgical thrombectomy, or superior vena caval filter for the initial treatment of upper extremity DVT

- In selected patients with acute upper-extremity DVT, eg, those with failure of anticoagulant or thrombolytic treatment and persistent symptoms, surgical embolectomy (Grade C) or catheter extraction (Grade C) should be considered.

- In selected patients with acute upper-extremity DVT, eg, those in whom anticoagulant treatment is contraindicated, a superior vena caval filter (Grade C) could be considered for initial treatment.

Anticoagulants for the long-term treatment of upper extremity DVT

- For patients with acute upper-extremity DVT, long-term treatment with a VKA (Grade B) is recommended.

Remark: As for acute DVT of the leg (section 2.1), a similar process should be considered for determining the duration of VKA treatment.

Elastic bandages for the long-term treatment of upper extremity DVT

- In patients with upper-extremity DVT who have persistent edema and pain, elastic bandages for symptomatic relief (Grade C) should be considered.

Antithrombotic Therapy in Peripheral Arterial Occlusive Disease

Recommendations

Preamble: For patients with clinical evidence of cerebrovascular disease or coronary artery disease, the recommendation for aspirin use is grade 1A. The following recommendations refer to patients who do **not** have evidence of cerebrovascular disease or coronary artery disease.

Summary of Recommendations

Chronic Limb Ischemia

Antiplatelet therapy

Aspirin

- Lifelong aspirin therapy, 75 to 300 mg/d, in comparison to no antiplatelet therapy in patients with clinically manifest coronary or cerebrovascular disease (Grade A) and in those without clinically manifest coronary or cerebrovascular disease (Grade A) is recommended. Clopidogrel over ticlopidine Grade B) is recommended.

Clopidogrel

- Clopidogrel in comparison to no antiplatelet therapy (Grade B) is recommended, but suggest that aspirin be used instead of clopidogrel (Grade B).

Cilostazol

- For patients with disabling intermittent claudication who do not respond to conservative measures (risk factor modification and exercise therapy) and who are not candidates for surgical or catheter-based intervention, can be given cilostazol (Grade

B).Clinicians should not use cilostazol in those with less-disabling claudication (Grade B).

Pentoxifylline

· The use of pentoxifylline (Grade A) is not recommended.

Prostaglandins

· For limb ischemia, clinicians should not use prostaglandins (Grade C).

Other agents

· In patients with intermittent claudication, the use of anticoagulants is not recommended (Grade A).

Acute Limb Ischemia

Heparin

· In patients with acute arterial emboli or thrombosis, treatment with immediate systemic anticoagulation with UFH to prevent thrombotic propagation is recommended (Grade B). Systemic anticoagulation with UFH followed by long-term VKA to prevent recurrent embolism in patients undergoing embolectomy is also recommended (Grade B).

Thrombolysis

· In patients with short-term (<14 days) thrombotic or embolic disease with low risk of myonecrosis and ischemic nerve damage developing during the time to achieve revascularization by this method, intra-arterial thrombolytic therapy should be considered(Grade C).

Vascular Grafts

Intraoperative anticoagulation during vascular reconstructions

- For patients undergoing major vascular reconstructive procedures, it is recommended that UFH should be given at the time of application of vascular cross-clamps (Grade A).

Prolonging the patency of grafts

Antiplatelet agents

- In patients undergoing prosthetic infrainguinal bypass, aspirin is recommended (Grade A).

Vitamin K antagonists

- VKA not be used routinely in patients undergoing infrainguinal, femoropopliteal or distal vein bypass (Grade B).

VKA plus aspirin

- For routine patients undergoing infrainguinal bypass without special risk factors for occlusion, VKA plus aspirin should not be used (Grade A). For those at high risk of bypass occlusion and limb loss, VKA plus aspirin may be considered (Grade C).

Carotid Endarterectomy

Aspirin

- Aspirin, 75 to 300 mg/d, be given preoperatively and continued indefinitely in patients undergoing carotid endarterectomy is recommended (Grade A).

Asymptomatic and Recurrent Carotid Stenosis

- In nonoperative patients with asymptomatic or recurrent carotid stenosis, lifelong aspirin, 75 to 150 mg/d is recommended (Grade B).

Lower Extremity Endovascular Procedures

- For all patients undergoing lower-extremity balloon angioplasty (with or without stenting), long-term aspirin, 75 to 150 mg/d is recommended (Grade B).

Antithrombotic Therapy in Patients With Saphenous Vein and Internal Mammary Artery Bypass Grafts

Saphenous Vein Bypass Grafting

- For patients who undergo saphenous vein bypass grafting for coronary artery disease, life-long aspirin therapy is recommended (grade A). Aspirin therapy, 300 mg/d, starting 6 h after operation for 1 year to reduce the frequency of saphenous vein bypass graft closure is recommended (grade A).

- If bleeding prevents the administration of aspirin at 6 h after surgery, aspirin therapy should be started as soon as possible thereafter (grade A).

- For patients allergic to aspirin, clopidogrel, 300 mg, as a loading dose 6 h after operation followed by 50 to 100 mg daily po is recommended (grade C).

- It is recommended that oral anticoagulants alone or in combination with aspirin should be considered after coronary artery bypass surgery in patients in whom oral anticoagulants are simultaneously indicated, for example, because of heart valve replacement (grade C).

Internal Mammary Artery Bypass Grafting

- For patients who undergo internal mammary artery bypass grafting for coronary artery disease, life-long aspirin therapy is recommended (grade A). Aspirin has not been shown to be beneficial in maintaining internal mammary artery bypass graft patency, and aspirin is not recommended if other diagnoses prompted internal mammary artery bypass grafting (grade C).

3. Use of Antithrombotic Agents During Pregnancy

When describing the various regimens of UFH and LMWH, we will use the following short forms:

- Minidose UFH: UFH 5,000 U SC q12h
- Moderate-dose UFH: UFH SC q12h in doses adjusted to target an anti-Xa level of 0.1to 0.3 U/mL.
- Adjusted-dose UFH: UFH SC q12h in doses adjusted to target a mid-interval aPTT into the therapeutic range.
- Prophylactic LMWH: eg, dalteparin 5,000 U SC q24h, or enoxaparin 40 mg SC q24 h (although at extremes of body weight modification of dose may be required).
- Intermediate-dose LMWH: eg, dalteparin 5,000 U SC q12h, or enoxaparin 40 mg SC q12h.
- Adjusted-dose LMWH: weight-adjusted, full-treatment doses of LMWH administered once or twice daily (eg, dalteparin 200 U/kg, or tinzaparin 175 U/kg qd, or dalteparin 100 U/kg q12h, or enoxaparin 1 mg/kg q12 h). As the half-life of LMWH is shorter in pregnancy, twicedaily dosing is preferable, at least in the initial treatment phase.
- Postpartum anticoagulants: warfarin for 4 to 6 weeks with a target INR of 2.0 to 3.0, with initial UFH or LMWH overlap until the INR is >2.0.
- In addition, the term surveillance refers to clinical vigilance and aggressive investigation of women with symptoms suspicious of DVT or PE.

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

- For women requiring long-term VKA therapy who are attempting pregnancy, frequent pregnancy tests should be performed and substituting UFH or LMWH for warfarin when pregnancy is achieved (Grade C).

Treatment of VTE During Pregnancy

- In women with acute VTE, either adjusted-dose LMWH throughout pregnancy or IV UFH (bolus followed by a continuous infusion to maintain the aPTT in the therapeutic range) for at least 5 days, followed by adjusted-dose UFH or LMWH for the remainder of the pregnancy is recommended. Anticoagulants should be administered for at least 6 weeks postpartum (Grade A).
- In women receiving adjusted-dose LMWH or UFH therapy, discontinuing the heparin 24 h prior to elective induction of labor (Grade B) is recommended.

Prevention of VTE During Pregnancy

Prior VTE and pregnancy

- In patients with a single episode of VTE associated with a transient risk factor that is no longer present, clinical surveillance and postpartum anticoagulants (Grade B) is recommended. If the previous event is pregnancy or estrogen-related or there are additional risk factors (such as obesity), antenatal anticoagulant prophylaxis (Grade C) should be considered.
- In patients with a single idiopathic episode of VTE who are not receiving long-term anticoagulants, prophylactic LMWH, or minidose UFH, or moderate-dose UFH, or clinical surveillance plus postpartum anticoagulants (Grade C) should be considered.
- In patients with a single episode of VTE and thrombophilia (confirmed laboratory abnormality) or strong family history of thrombosis and not receiving long-term anticoagulants, prophylactic or intermediate-dose LMWH, or mini-dose or moderatedose UFH, plus postpartum anticoagulants should be considered (Grade C).
- In antithrombin-deficient women, compound heterozygotes for prothrombin G20210A and factor V Leiden and homozygotes for these conditions

with a history of VTE, intermediate-dose LMWH prophylaxis or moderate-dose UFH (Grade C) should be considered.

- In patients with multiple (two or more) episodes of VTE and/or women receiving long-term anticoagulants (eg, single episode of VTE—either idiopathic or associated with thrombophilia) adjusted-dose UFH or adjusted-dose LMWH followed by resumption of longterm anticoagulants postpartum (Grade C) should be considered.
- In all women with previous DVT, antenatally and postpartum, use of graduated elastic compression stockings (Grade C) should be considered.

Thrombophilia and venous thromboembolism associated with pregnancy

- In antithrombin-deficient women, compound heterozygotes for prothrombin G20210A and factor V Leiden, and homozygotes for these conditions with no prior VTE, active prophylaxis (Grade C) should be considered.
- In all other patients with no prior VTE and thrombophilia (confirmed laboratory abnormality), surveillance or prophylactic LMWH or minidose UFH, plus postpartum anticoagulants (Grade C) should be considered.

Thrombophilia and Pregnancy Complications

- For women with recurrent pregnancy loss (three or more miscarriages) and women with prior severe or recurrent preeclampsia, abruptions, or otherwise unexplained intrauterine death, screening for congenital thrombophilia and APLAs (Grade C) should be considered.
- For pregnant patients with APLAs and a history of multiple (two or more) early pregnancy losses or one or more late pregnancy losses, preeclampsia, IUGR, or abruption, administration of antepartum aspirin plus minidose or moderate-dose UFH or prophylactic

LMWH (Grade C) should be considered..

- For women with a congenital thrombophilic deficit and recurrent miscarriages, a second-trimester or later loss, severe or recurrent preeclampsia, or abruption, low-dose aspirin therapy plus either minidose heparin or prophylactic LMWH therapy (Grade C) should be considered. Consider postpartum anticoagulants to be administered to these women (Grade C).

- Patients with APLAs and a history of venous thrombosis are usually receiving long-term oral anticoagulation therapy because of the high risk of recurrence. During pregnancy, adjusted-dose LMWH or UFH therapy plus low-dose aspirin and resumption of long-term oral anticoagulation therapy postpartum (Grade B) is recommended.

- Patients with APLAs and no prior VTE or pregnancy loss should be considered to have an increased risk for the development of venous thrombosis and, perhaps, pregnancy loss. Consider one of the following approaches for these women: surveillance, mini-dose heparin, prophylactic LMWH, and/or low-dose aspirin, 75 to 162 mg daily (all Grade C).

Prophylaxis in Patients with Mechanical Heart Valves

In women with prosthetic heart valves, the following are recommended:

- Adjusted-dose, twice-daily LMWH throughout pregnancy in doses adjusted either to keep a 4-h postinjection anti-Xa heparin level at approximately 1.0 to 1.2 U/mL (preferable) or according to weight (Grade B), or

- Aggressive adjusted-dose UFH throughout pregnancy: ie, administered SC q12h in doses adjusted to keep the mid-interval aPTT at least twice control or to attain an anti-Xa heparin level of 0.35 to 0.70 U/mL (Grade B), or

- UFH or LMWH (as above) until the thirteenth week, change to warfarin until the middle of the third trimester, and then restart UFH or LMWH (Grade B).

Remark: Long-term anticoagulants should be resumed postpartum with all regimens.

- In women with prosthetic heart valves at high risk, the addition of low-dose aspirin, 75 to 150 mg/d (Grade C) should be considered.

4. Managing Oral Anticoagulant Therapy

Indications for Oral Anticoagulant Therapy

- Prevention of Venous Thromboembolism
- Treatment of DVT
- Primary Prevention of Ischemic Coronary Events
- AMI
- Prosthetic Heart Valves
- Atrial Fibrillation

Other Indications for Oral Anticoagulant Therapy

There are other widely accepted indications for oral anticoagulant therapy that have not been evaluated in properly designed clinical trials. These indications include

- atrial fibrillation associated with valvular heart disease
- mitral stenosis in the presence of sinus rhythm.
- Other valvular heart disease.
- Long-term anticoagulation (INR 2.0 to 3.0) also is indicated in patients who have sustained one or more episodes of systemic thromboembolism.
- Anticoagulants are not presently indicated in patients with ischemic cerebrovascular disease.
- Reduced left ventricular systolic function is associated with both stroke and mortality even in the absence of documented atrial fibrillation. Warfarin is used frequently in patients with dilated cardiomyopathy, although no randomized trials have confirmed the benefit of anticoagulation.
- Long-term anticoagulant therapy also is indicated in patients with ischemic stroke of unknown origin who have a combination of a patent foramen ovale and atrial septal aneurysm because these patients have an increased the risk of recurrent stroke despite treatment with aspirin.

Warfarin dosing may be separated into initial and maintenance phases. After treatment is started, the INR response is monitored frequently until a stable dose-response relationship is obtained; thereafter, the frequency of INR testing is reduced.

Initiating and monitoring warfarin therapy

Therapy with warfarin is initiated by giving the patient 5-10 mg in the evening for the first two nights (2.5 mg in those over 75 years) and adjusting the dose to achieve an adequate prothrombin time. Although the use of a 10 mg loading dose has been traditional in the past, for most people this is too much. Most trials show that using a 10 mg loading dose causes one to overshoot and leads to a delay in achieving a stable therapeutic INR. A practical approach is to use 5mg in loading patients over the age of 50 or in patients with albumin under three and 10 mg in other patients. The elderly patient (over age 75) may only need a 2.5 mg loading dose. Nomograms for 5 and 10mg warfarin loading doses are given in Table 1. The effect of warfarin on the INR takes 36 hours to occur so the morning INR reflects the effect of the warfarin dose 36 hours before. Factor VII has the shortest half-life and so it is the first factor reduced as a result of warfarin therapy. However, the full anticoagulant effect does not occur until there is a reduction in prothrombin (factor II) and factor X, which may take several days. Thus, in acute thrombosis

Recommended Therapeutic Range for Oral Anticoagulant Therapy

Indication	Target (desired range) of INR
Prophylaxis of central venous catheter thrombosis	Minidose warfarin (1 mg/day) with no routine INR monitoring
Prophylaxis of thrombosis during stage IV breast cancer chemotherapy Primary Prophylaxis of myocardial infarction in high risk men or women	1.6 (1.3-1.9)
Prophylaxis of venous thromboembolism in high risk patients Treatment of venous thromboembolism Prophylaxis of cardiac thromboembolism • atrial fibrillation • heart valve disease, heart failure, cardiomyopathy	2.5 (2.0-3.0)
mechanical heart valves • first generation • second generation	3.5 (3.0-4.5) 3.0 (2.5-3.5)
• bioprosthetic heart valves (selected patients) • acute myocardial infarction (selected patients) Prophylaxis of recurrent myocardial infarction (selected patients) Critical limb ischaemia	2.5 (2.0-3.0)
Prophylaxis of recurring venous, cardiac or arterial thromboembolism	2.5 (2.0-3.0) (± aspirin) or 3.5 (3.0-4.0) (± aspirin)

heparin needs to be continued for at least 24 hours after the prothrombin time is therapeutic to allow for factors II and X to fall. For chronic indications such as atrial fibrillation, warfarin can be started at lower daily doses (2.5-5.0 mg). This allows for initiation of warfarin therapy without the use of heparin. The INR is usually checked daily until the therapeutic range has been reached and sustained for 2 consecutive days.

Maintenance phase

Table 2 gives guidelines for adjusting warfarin doses in patients once therapeutic prothrombin times have been reached. Once the INR becomes stable, the frequency of testing can be reduced to intervals as long as 4 weeks. When dose adjustments are required,

frequent monitoring is resumed. Some patients on long-term warfarin therapy experience unexpected fluctuations in dose-response due to changes in diet, concurrent medication changes, poor compliance, or alcohol consumption.

Since warfarin is metabolized in the liver by the cytochrome P450 system, the INR may change with starting or stopping other medications that affect CYP2C9. Multiple agents can augment or decrease warfarin effect and are listed in table 3. Unfortunately, many drugs may have an unpredictable effect on the INR. The most prudent strategy is to check the INR several days after starting a new drug and then weekly to ensure the INR is stable. If the patient is started on a drug which results in predictable changes in the INR, then the warfarin dose may be adjusted, usually by 50%, when starting that drug. Vitamin K is found in many foods (table 4), especially green vegetables. Patients will often avoid any vegetables due to fear of reversing their anticoagulation. This will result in those patients having lower vitamin K stores and will make them prone to unstable INRs. Patients should be instructed that **consistency** of diet is more important than avoiding vitamin K. A diet rich in vegetables and fruits is beneficial, especially for patients being anticoagulated, and should be encouraged. Patients should be advised of the vitamin K content of common foods and should be encouraged to be consistent with their diet.

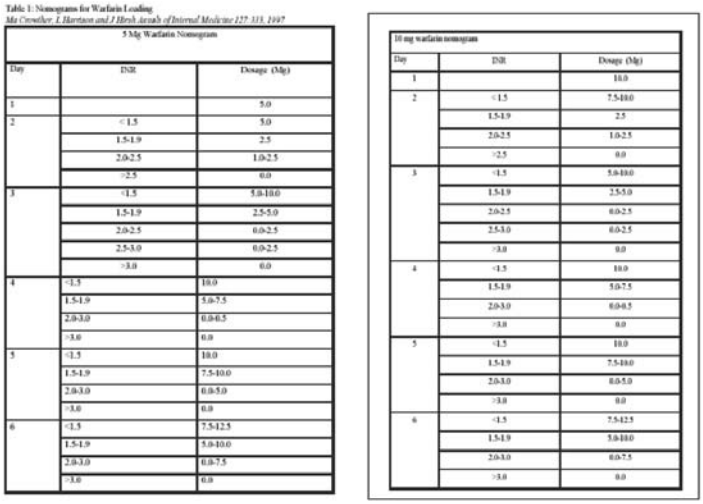


Table 1: Nomograms for Warfarin Loading
Ma Cmwelher, L Harrison and J Hirsh Annals of Internal Medicine 127: 333, 1997

5 Mg Warfarin Nomogram

Day	INR	Dosage (Mg)
1		5.0
2	< 1.5	5.0
	1.5-1.9	2.5
	2.0-2.5	1.0-2.5
	>2.5	0.0
3	<1.5	5.0-10.0
	1.5-1.9	2.5-5.0
	2.0-2.5	0.0-2.5
	2.5-3.0	0.0-2.5
	>3.0	0.0
4	<1.5	10.0
	1.5-1.9	5.0-7.5
	2.0-3.0	0.0-0.5
	>3.0	0.0
5	<1.5	10.0
	1.5-1.9	7.5-10.0
	2.0-3.0	0.0-5.0
	>3.0	0.0
6	<1.5	7.5-12.5
	1.5-1.9	5.0-10.0
	2.0-3.0	0.0-7.5
	>3.0	0.0

10 mg warfarin nomogram

Day	INR	Dosage (Mg)
1		10.0
2	<1.5	7.5-10.0
	1.5-1.9	2.5
	2.0-2.5	1.0-2.5
	>2.5	0.0
3	<1.5	5.0-10.0
	1.5-1.9	2.5-5.0
	2.0-2.5	0.0-2.5
	2.5-3.0	0.0-2.5
	>3.0	0.0
4	<1.5	10.0
	1.5-1.9	5.0-7.5
	2.0-3.0	0.0-0.5
	>3.0	0.0
5	<1.5	10.0
	1.5-1.9	7.5-10.0
	2.0-3.0	0.0-5.0
	>3.0	0.0
6	<1.5	7.5-12.5
	1.5-1.9	5.0-10.0
	2.0-3.0	0.0-7.5
	>3.0	0.0

Table 2: Maintenance Warfarin Adjustment Nomogram (*Hatheway and Goodnight*)

INR Dose Change

1.1-1.4 Day 1:	Add 10-20% total weekly dose (TWD)*
	Weekly: Increase TWD by 10-20%
	Return: 1 Week
1.5-1.9 Day 1:	Add 5-10% of TWD
	Weekly: Increase Twd by 5-10%
	Return: 2 Weeks
2.0-3.0	No Change
	Return: 4 Weeks
3.1-3.9 Day 1:	Subtract 5-10% TWD
	Weekly: Reduce TWD by 10-20%
	Return: 2 Weeks
4.0-5.0 Day 1:	No Warfarin
	Weekly: Reduce TWD by 10-20%
	Return: 1 Week
> 5.0	Stop Warfarin until INR <3.0
	Decrease TWD by 20-50%
	Return Daily

*TWD = Total Weekly Dose

Recommendations

Practical Dosing

1. For the initiation of and maintenance dosing of warfarin, commence therapy with an average maintenance dose of 5 mg (grade 2A compared to a dose of 10 mg). Starting doses of 5 mg might be appropriate for elderly patients, patients with impaired nutrition or liver disease, and in patients with a high risk for bleeding.

Models of Anticoagulation Management

The effectiveness and safety of warfarin are critically dependent on maintaining the INR in the therapeutic range. This objective is facilitated by aiming for an INR that is in the middle of the INR range (ie, a goal of 2.5 for a designated range of 2.0 to 3.0, and a goal of 3.0 for a designated range of 2.5 to 3.5). The majority of the events (both thromboembolic and bleeding) occur when the PT ratio is outside the designated therapeutic range and that both the safety and efficacy of warfarin are increased by maintaining good anticoagulant control.

Recommendations

1. In comparing UC (usual care) with AMS, it is recommended that clinicians employ a systematic process to manage oral anticoagulation dosing that includes a knowledgeable provider, reliable PT monitoring, and an organized system of follow-up, patient communication, and education (grade B).
2. Computer software programs for dose management must be considered individually based on well-designed clinical outcome studies. Consideration of those software programs demonstrated to provide dosing decisions equivalent to a better than physician management, is recommended especially in high-volume anticoagulation programs (grade C).

Management of Nontherapeutic INRs

1. For patients with INRs greater than the therapeutic level but <5.0 who do not have significant bleeding, lower the dose or omit a dose and resume therapy at a lower dose when the INR is at the therapeutic level. If the INR is only minimally greater than the therapeutic range, no dose reduction may be required (grade C).
2. For patients with INRs >5.0 but <9.0 with no significant bleeding, omit the next one or two doses, monitor the INR more frequently, and resume therapy at a lower dose when the INR is at the therapeutic level.

Alternatively, omit the dose and administer vitamin K1, 1 to 2.5 mg orally, particularly if the patient is at increased risk of bleeding. If more rapid reversal is required because the patient requires urgent surgery, administer vitamin K1, 2 to 4 mg orally, with the expectation that a reduction of the INR will occur in 24 h. If the INR is still high, administer an additional dose of vitamin K1, 1 to 2 mg orally (all grade C compared with no treatment).

3. For patients with INRs >9.0 with no significant bleeding, hold off on warfarin therapy and administer a higher dose of vitamin K1, 3 to 5 mg orally, with the expectation that the INR will be reduced substantially in 24 to 48 h. Monitor the INR more frequently and administer additional vitamin K1 if necessary. Resume therapy at a lower dose when the INR reaches the therapeutic level (all grade C compared with no treatment).
4. For patients with INRs >20 with serious bleeding, hold off on warfarin therapy and administer vitamin K1, 10 mg by slow IV infusion, supplemented with fresh plasma or prothrombin complex concentrate, depending on the urgency of the situation. Administration of vitamin K1 can be repeated every 12 h (grade C).
5. For patients with life-threatening bleeding, hold off on warfarin therapy and administer prothrombin complex concentrate supplemented with vitamin K1, 10 mg by slow IV infusion. Repeat this treatment as necessary, depending on the INR (grade C).

If the continuation of warfarin therapy is indicated after the administration of high doses of vitamin K1, then heparin can be given until the effects of vitamin K1 have been reversed and the patient becomes responsive to warfarin.

Management of Oral Anticoagulation During Invasive Procedures

Strategy for perioperative anticoagulation

The anticoagulation strategy selected depends upon an evaluation of the thromoembolic risk and the haemorrhagic risk of the surgical procedure.

Minor procedures

Oral anticoagulants may be continued at a lower therapeutic level (INR 1.5-1.8) for minor procedures with a low risk of bleeding. These include excision of skin lesions, bone marrow biopsies, cataract surgery and procedures in which the bleeding can be controlled readily by local measures. This approach is not recommended for laparoscopic surgery and ultrasound or CT-guided biopsies.

Major procedures

The strategy for perioperative anticoagulation in patients undergoing major surgery is based more on the assessment of the risk of thromboembolism than the risk of haemorrhage. Patients can be divided into two risk groups (Table 1). In the low-risk group warfarin is withheld for five days before surgery, but no alternate anticoagulation is given (Table 2). High-risk patients should receive aggressive alternate anticoagulation with unfractionated or low molecular weight heparin (Table 2). Low molecular weight heparins are commonly used as prophylaxis against venous thromboembolism prior to and after major surgery. They are more effective than low dose heparin in orthopaedic patients who are at high risk for venous thromboembolism. Low molecular weight heparins do not increase the risk of bleeding any more than low dose heparin and are more convenient to use, as laboratory monitoring is generally not required.

There is considerable variability amongst individual surgeons as to an acceptable upper limit of the INR on the day of surgery. In particular, neurosurgeons generally prefer a near normal INR, while vascular surgeons may accept an INR of 1.5-2.0.

Anaesthetic considerations

There are concerns about the possibility of extradural haematoma formation in patients receiving heparin and undergoing epidural/spinal anaesthesia. Unfractionated heparin should be ceased at least six hours prior to such an anaesthetic and low molecular weight heparin ceased a minimum of 12 hours (and preferably 16-18 hours) before hand, at which time anti-Xa values (the best laboratory test for activity of such heparins) fall to low levels. A longer delay is advisable in patients with renal insufficiency in whom excretion of low molecular weight heparin is reduced. If a low molecular weight heparin is used the night prior to epidural/spinal anaesthesia planned for the next morning, the dose preferably should be the thromboprophylactic dose rather than the full anticoagulation dose.

Table 1 Risk of thromboembolism if anticoagulation is withdrawn

	Low	High
Atrial fibrillation And/or cardiomyopathy	Without stroke or Systemic embolisation in	With stoke or systemic embolisation within the last 12 months
Biological heart valves Prosthesis	The last 12 months Except during first three months	During first three months Cardiac mechanical
Venous thrombosis	Vascular grafts	valves (mitral>aortic) *within the last three
Systemic arterial emboli	Not within the last three months and without a confirmed hypercoagulable state Non-recurrent	months, or recurrent venous thrombosis Recurrent

Note: two low-risk factors = high risk

- The risk in patients with a confirmed hypercoagulable state but no venous thrombosis within previous three months, and no recurrent thrombosis, has not been established.
- Intermediate: neither low nor high

The recommendations

1. For patients with low risk of thromboembolism (eg, patients without venous thromboembolism for >3 months or patients who have experienced atrial fibrillation who do not have a history of stroke), stop warfarin therapy approximately 4 days before surgery, allow the INR to return to a near-normal level, briefly administer postoperative prophylaxis (if the intervention itself creates a higher risk of thrombosis) using low-dose heparin, 5,000 U SC, and simultaneously begin warfarin therapy (grade C).

2. For patients with intermediate risk of thromboembolism, stop warfarin therapy approximately 4 days before surgery, allow the INR to fall, cover the patient with low-dose heparin, 5,000 U SC, beginning 2 days before surgery or with a prophylactic dose of LMWH, and then commence low-dose heparin (or LMWH) and warfarin therapy after surgery (grade C).

3. For patients with high risk of thromboembolism (eg, patients with a recent [<3 months] history of venous thromboembolism, patients with a mechanical cardiac valve in the mitral position; or an old model of cardiac valve [ball/cage]), stop warfarin therapy approximately 4 days before surgery, allow the INR to return to a normal level, begin therapy with full-dose heparin or full-dose LMWH as the INR falls (approximately 2 days before surgery). Heparin can be administered as an SC injection on an outpatient basis, can then be given as a continuous IV infusion after hospital admission in preparation for surgery, and can be discontinued 5 h before surgery with the expectation that the anticoagulant effect will have worn off at the time of surgery. It is also possible to continue the administration of SC heparin or LMWH and to stop therapy 12 to 24 h before surgery with the expectation that the anticoagulant effect will be very low or will have worn off by the time of surgery (all grade C).

Post-surgical;

Once haemostasis secured, and generally after at least six hours post surgery:

- Recommence full dose LMWH (preferred) or UFH (do not commence with bolus dose)
- Start warfarin as soon as oral fluids tolerated using the preoperative maintenance dose. A lower dose may be required if INR >1.2 or if other drugs are being used.
- Cease UFH/LMWH when INR>2.0 on at least two consecutive days

If patient discharged before INR >2.0, use LMWH as an outpatient

4. For patients with low risk of bleeding, continue warfarin therapy at a lower dose and operate at an INR of 1.3 to 1.5, an intensity that has been shown to be safe in randomized trials of gynecologic and orthopedic surgical patients. The dose of warfarin can be lowered 4 or 5 days before surgery. Warfarin therapy then can be restarted after surgery and supplemented with low-dose heparin, 5,000 U SC, if necessary (grade C).

5. For patients undergoing dental procedures who are not considered to be at high risk for bleeding, we recommend that warfarin therapy not be discontinued. In patients at high risk for bleeding, we recommend that warfarin therapy be discontinued (all grade C).

6. For patients undergoing dental procedures in whom local bleeding must be controlled, tranexamic acid or epsilon amino caproic acid mouthwash can be administered without interrupting anticoagulant therapy (grade C).

Approach to dental surgery

1. Check INR the day before the procedure to ensure it is within the therapeutic range for the patient. If above this, delay surgery until the INR is within the therapeutic range.

2. In the majority of cases, continue warfarin therapy throughout the dental procedure and postoperative period. This may need to be reassessed for multiple and complex dental extractions, particularly if infection is a concern, in which case an INR of under 1.6 may be desirable.

3. Daily or alternate day monitoring of the INR may be required, especially if the patient is receiving antibiotics.

4. Judicious use of local measures to ensure adequate haemostasis, e.g. packs soaked in 5% tranexamic acid placed over the extraction site.

5. In patients with excessive oozing, tranexamic acid mouthwash (10ml of 5% solution) held in the mouth for two minutes is helpful when used six hourly for 3-5 days. Practically, this preparation may be difficult to obtain other than from major teaching hospital pharmacies.

Instructions for patients on warfarin for multiple and complicated surgical tooth extraction *

1. Cease your warfarin two nights before procedure and do not take it again until the evening of the day on which you have the extraction.

2. Have an INR test performed on the morning of the extraction before the procedure. This result will be telephoned to your dentist.

3. If the INR is >1.6 (normal <1.3), it is suggested that, if possible, the extraction be deferred for another occasion.

4. Start taking warfarin tablets again the night after the procedure, with the same dosage you had been taking previously before the extraction, and continue each day until the next INR test.

5. If you are prescribed antibiotics, for the procedure, have an INR test 3-4 days afterwards to check warfarin dose. Do this earlier is excessive bleeding occurs.

Dental procedures of a less traumatic nature, provided infections not present, generally do not require alterations in warfarin dosage.

5. Heparin and Low-Molecular-Weight Heparin

Heparin and its derivative, low-molecular-weight heparin (LMWH), are the anticoagulants of choice when a rapid anticoagulant effect is required, because their onset of action is immediate when administered by IV injection. Both types of heparins are administered in lower doses for primary prophylaxis than for treatment of venous thrombosis or acute myocardial ischemia. Heparin has pharmacokinetic limitations not shared by LMWHs. Based on these pharmacokinetic limitations, heparin therapy is usually restricted to the hospital setting, where its effect can be monitored and its dosage adjusted frequently. In contrast, LMWH preparations can be administered in either the in-hospital or out-of-hospital setting because they can be administered subcutaneously (sc) without the need for laboratory monitoring. When long-term anticoagulant therapy is indicated, heparin or LMWH administration is usually followed by treatment with oral anticoagulants. However, long-term out-of-hospital treatment with heparin or LMWH is used when anticoagulant therapy is indicated in pregnancy and in patients who develop recurrent venous thromboembolism while treated with appropriate doses of oral anticoagulants.

Clinical Indications

Heparin is effective and indicated

- for the prevention of venous thromboembolism;
- for the treatment of venous thrombosis and pulmonary embolism (PE);
- for the early treatment of patients with UA and acute myocardial infarction (MI);
- for patients who undergo cardiac surgery using cardiac bypass, vascular surgery, and coronary angioplasty;
- for patients with coronary stents
- in selected patients with disseminated intravascular coagulation.

LMWHs are effective and indicated for

- the prevention of venous thromboembolism
- the treatment of venous thrombosis, for the treatment of acute PE
- the early treatment of patients with UA.

INDICATIONS FOR PARENTERAL ANTICOAGULATION WITH HEPARINS

Low dose unfractionated heparin
▪ Local prevention of clotting in peripheral arterial catheters
▪ DVT prophylaxis
Routine 5000 IU 8-12 hourly or 7500 12 hourly by subcutaneous injection Monitoring of APTT nor routinely required [5]
Adjusted to maintain target APTT ratio (monitor) e.g. hip surgery, pregnancy [5]
Full dose unfractionated heparin (APTT should be monitored)
▪ Treatment of acute deep vein thrombosis and/or pulmonary embolism; and maintenance of anticoagulation to prevent recurrence in selected patients
▪ Prophylaxis of cardiac thromboembolism in selected patients
▪ Severe unstable angina, selected patients with acute myocardial infarction
▪ Coronary angioplasty or bypass surgery
▪ Acute critical limb ischaemia
▪ Peripheral angioplasty or bypass surgery
▪ Carotid endarterectomy
▪ Haemodialysis
Low dose low molecular weight heparin (monitoring of anti-Xa not routinely required)
▪ DVT prophylaxis
Full dose low molecular weight heparin (monitoring of anti-Xa not routinely required)
▪ Treatment of acute deep vein thrombosis and/or pulmonary embolism
▪ Severe unstable angina
▪ DVT prophylaxis in selected patients

Laboratory Monitoring

There is a relationship among heparin dose, efficacy and safety. Since the anticoagulant response to heparin varies among patients with thromboembolic disorders it is standard practice to adjust the dose of heparin and monitor its effect by measurement of the APTT that is sensitive to the inhibitory effects of heparin on thrombin, factor Xa, and factor IXa. Although a relationship exists between heparin dose and therapeutic efficacy for patients with venous thromboembolism, such a relationship has not been established for patients with acute coronary ischemia, although those receiving concomitant thrombolytic therapy or glycoprotein (GP) IIb/IIIa (GPIIb/IIIa) antagonists given heparin in a dose used to treat venous thrombosis have an unacceptably high rate of bleeding.

The risk of heparin-associated bleeding increases with dose and with concomitant thrombolytic therapy or the GPIIb/IIIa antagonist abciximab. The risk of bleeding is also increased by recent surgery, trauma, invasive procedures, or concomitant hemostatic defects.

Despite its limitations, the APTT remains the most frequently used method for monitoring the anticoagulant response to heparin. **The APTT should be measured approximately 6 h after the bolus dose of heparin and the continuous IV dose should be adjusted based on the result.**
When heparin is given by sc injection in a dose of 35,000 U/24 h in two divided doses, the anticoagulant effect is delayed for approximately 1 h and peak plasma levels occur at approximately 3 h.

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.*

Dosing Nomograms

A number of methods for standardizing the management of IV heparin therapy have been published, including heparin dose-adjustment nomograms and computer algorithms.

When a nomogram is used, it is important to determine the appropriate therapeutic range based on the local laboratory reagent and to adapt the recommended dosage adjustments accordingly. For patients with venous thrombosis or PE, the targeted APTT should be equivalent to a heparin level or 0.3 to 0.7U/mL by antifactor Xa heparin levels. A lower therapeutic range is recommended for patients with acute myocardial ischemia receiving thrombolytic or GPIIb/IIIa antagonist agents, since a lower dose of heparin proved safer and no less effective in these circumstances than the higher-dose regimen established for patients with venous thrombosis. Recognizing that the traditional heparin dosing regimens cause excessive bleeding in patients with acute MI who receive thrombolytic therapy, a therapeutic range corresponding to antifactor Xa levels of 0.14 to 0.34 seems reasonable. Failure to adapt nomograms to the therapeutic range could result in dangerous errors in heparin therapy.

Figure7.Weight-based nomogram

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.*

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.*

Heparin Resistance

Some patients require higher-than-average doses of heparin to prolong APTT to the therapeutic range. These patients are designated heparin resistant if their daily heparin requirement is >35,000 U/24 h and approximately 25% of patients with venous thromboembolism fulfill this criterion. Heparin resistance has been associated with AT deficiency, increased heparin clearance, elevations in heparin binding proteins, and elevations of factor VIII, fibrinogen and platelet factor 4.

Adjusting dosage by anti-Xa heparin concentrations results in favorable clinical outcomes in heparin resistant patients despite lower doses of heparin and sub therapeutic APTT levels.

For patients who require >35,000 U of UFH per 24 h, the dose should be adjusted to maintain anti-Xa heparin levels of 0.35 to 0.70 IU/mL.

The anticoagulant effect of heparin is modified by platelets, fibrin, vascular surfaces, and plasma proteins. Platelets limit the anticoagulant effect of heparin by protecting surface factor Xa from inhibition by heparin/AT and by secreting PF4, a heparin-neutralizing protein. Fibrin limits the anticoagulant effect of heparin by protecting fibrin-bound thrombin from inhibition by heparin/AT.

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).*

Overcoming the Anticoagulant Effect of Heparin

The anticoagulant effect of UFH can be neutralized rapidly by IV protamine, a cationic protein derived from fish sperm that binds strongly to (anionic) heparin in a ratio of approximately 100-U UFH per milligram of protamine; 50 mg of protamine would therefore be required immediately following a 5,000-U IV heparin bolus to counteract the anticoagulant effect. When infused, only the heparin given during the preceding

several hours should be included in the dose calculation, since the half-life of IV UFH is approximately 60 min. A patient receiving an infusion of 1,250 U/h needs approximately 30 mg of protamine. Neutralization of heparin after a sc dose may require a prolonged infusion or a repeated injection of protamine. A fall in APTT can be used to confirm heparin neutralization.

The risks of severe adverse reactions to protamine, such as hypotension and bradycardia, are reduced by slow administration over 1 to 3 min. Allergic reactions, including anaphylaxis, are associated with previous exposure to protamine-containing insulin, eg, neutral protamine hagedorn insulin, vasectomy, and hypersensitivity to fish. Patients at risk of developing antiprotamine antibodies can be pretreated with corticosteroid and antihistamine medications.

Protamine neutralizes the antithrombin activity of LMWH, normalizing the APTT and thrombin time, but the cationic protein neutralizes the antifactor Xa activity incompletely because protamine exhibits reduced binding to low-molecular-weight components. The clinical significance of incomplete anti-Xa neutralization by protamine is unclear. No published clinical studies demonstrate a beneficial effect of protamine on bleeding complications of LMWH.
Recommendations for treatment of LMWH overdose listed below are consistent with package labeling but are clinically untested. Within 8 h of administering LMWH, the dose of protamine is 1 mg/100 anti-Xa u for enoxaparin (1 mg = approximately 100 anti-Xa u). If bleeding continues, a second dose of 0.5 mg protamine/100 anti-Xa U LMWH may be administered. Smaller doses are needed beyond 8 h after LMWH administration.

6. Heparin-Induced Thrombocytopenia: Recognition, Treatment, and Prevention

Recognition of HIT

Platelet count monitoring for HIT

- For patients receiving heparin in whom the risk of HIT is considered to be <0.1%, platelet count monitoring over no platelet count monitoring (Grade B) is recommended.

Platelet count monitoring of patients recently treated with heparin

- For patients who are starting UFH or LMWH treatment and who have received UFH within the past 100 days, or those patients in whom exposure history is uncertain, consider obtaining a baseline platelet count and then a repeat platelet count within 24 h of starting heparin (Grade C).

Acute systemic reactions after IV UFH bolus

- For patients who acquire acute inflammatory, cardiorespiratory, neurologic, or other unusual symptoms and signs within 30 min following an IV UFH bolus, performing an immediate platelet count measurement, and comparing this value to recent prior platelet counts, in comparison with not performing a platelet count measure (Grade B) is recommended.

Platelet count monitoring in patients receiving therapeutic-dose UFH

- For patients who are receiving therapeutic-dose UFH, consider at least every-other-day platelet count monitoring until day 14, or until UFH is stopped, whichever occurs first (Grade C).

Platelet count monitoring in postoperative patients receiving UFH antithrombotic prophylaxis

- For patients who are receiving postoperative antithrombotic prophylaxis with UFH (HIT risk >1%), consider at least every-other-day platelet count

monitoring between postoperative days 4 to 14, or until UFH is stopped, whichever occurs first (Grade C).

Platelet count monitoring in patients in whom HIT is infrequent (0.1 to 1%)

- For medical/obstetrical patients who are receiving prophylactic-dose UFH, postoperative patients receiving prophylactic-dose LMWH, postoperative patients receiving intravascular catheter UFH "flushes," or medical/ obstetric patients receiving LMWH after first receiving
- UFH (HIT risk, 0.1 to 1%), consider platelet count monitoring every 2 or 3 days from day 4 to day 14 (or until heparin is stopped, whichever occurs first), when practical (Grade C).

Platelet count monitoring when HIT is rare (<0.1%)

- For medical/obstetric patients who are only receiving LMWH, or medical patients who are receiving only intravascular catheter UFH flushes (HIT risk <0.1%), clinicians should **not** use routine platelet count monitoring (Grade C).

When should HIT be suspected?

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

Special situation: anticoagulant prophylaxis and platelet count monitoring after cardiac surgery

- For postoperative cardiac surgery patients, excluding a diagnosis of HIT if the platelet count falls by >50% (and/ or a thrombotic event occurs) between postoperative days 4 to day 14 (day of cardiac surgery = day zero) (Grade B) is recommended.

Treatment of HIT

Nonheparin anticoagulants for HIT

- For patients with strongly suspected (or confirmed) HIT, whether or not complicated by thrombosis, use of an alternative, nonheparin anticoagulant, such as lepirudin (Grade 1C_), argatroban (Grade B), bivalirudin (Grade C), or danaparoid (Grade A), over further UFH or LMWH therapy, and over no further anticoagulation (with or without vena caval filter) is recommended.

- For patients with strongly suspected (or confirmed) HIT, whether or not there is clinical evidence of lower-limb DVT, routine ultrasonography of the lower-limb veins for investigation of DVT, over not performing routine ultrasonography (Grade B) is recommended .

VKAs

Management of DTI-VKA overlap

- For patients with strongly suspected or confirmed HIT, the use of vitamin K antagonist (coumarin) therapy until after the platelet count has substantially recovered (eg, to at least 100 x109/L, and preferably, 150 x109/L) is not recommended. ; VKA should be administered only during overlapping alternative anticoagulation (minimum 5-day overlap), and begun with low, maintenance doses (maximum, 5 mg, warfarin; 6 mg, phenprocoumon); the alternative anticoagulant should not be stopped until the platelet count has reached a stable plateau, and with at least the last 2 days the INR within the target therapeutic range (all Grade B).

Reversal of VKA anticoagulation

- For patients receiving VKAs at the time of diagnosis of HIT, use of vitamin K (Grade C) is recommended.

LMWH for HIT

- For patients with strongly suspected HIT, whether or not complicated by thrombosis, use of LMWH (Grade B) is not recommended.

Prophylactic platelet transfusions for HIT

- For patients with strongly-suspected or confirmed HIT who do not have active bleeding, prophylactic platelet transfusions not be administered (Grade C).

Special Patient Populations

Patients with previous HIT undergoing cardiac or vascular surgery

- For patients with a history of HIT who are HIT antibody negative and require cardiac surgery, the use of UFH over a nonheparin anticoagulant (Grade B) is recommended.

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

Patients with acute or subacute HIT undergoing cardiac surgery

- For patients with acute HIT (thrombocytopenic, HIT antibody positive) who require cardiac surgery, one of the following alternative anticoagulant approaches (in descending order of preference) is recommended: delaying surgery (if possible) until HIT antibodies are negative [Grade B]; using bivalirudin for intraoperative anticoagulation during cardiopulmonary bypass (if ecarin clotting time [ECT] available) [Grade B] or during off-pump cardiac surgery (Grade A); using lepirudin for intraoperative anticoagulation (if ecarin clotting time available and patient has normal renal function) [Grade B]; using UFH plus the antiplatelet agent, epoprostenol (if ECT monitoring not available or renal insufficiency

precludes lepirudin use) [Grade C]; using UFH plus the antiplatelet agent, tirofiban (Grade C); or using danaparoid for intraoperative anticoagulation (if anti-factor Xa levels are available) [Grade C].

- For patients with subacute HIT (platelet count recovery, but continuing HIT antibody-positive), delaying surgery (if possible) until HIT antibodies are negative and then using heparin is recommended. [Grade B]. Alternatively, consider the use of a nonheparin anticoagulant [Grade C].

PCIs

- For patients with acute or previous HIT who require cardiac catheterization or PCI, use of an alternative anticoagulant, such as argatroban (Grade B), bivalirudin (Grade B), lepirudin (Grade B), or danaparoid (Grade C), over the use of heparin is recommended.

Prevention of HIT

Reducing HIT antibody formation and clinical HIT

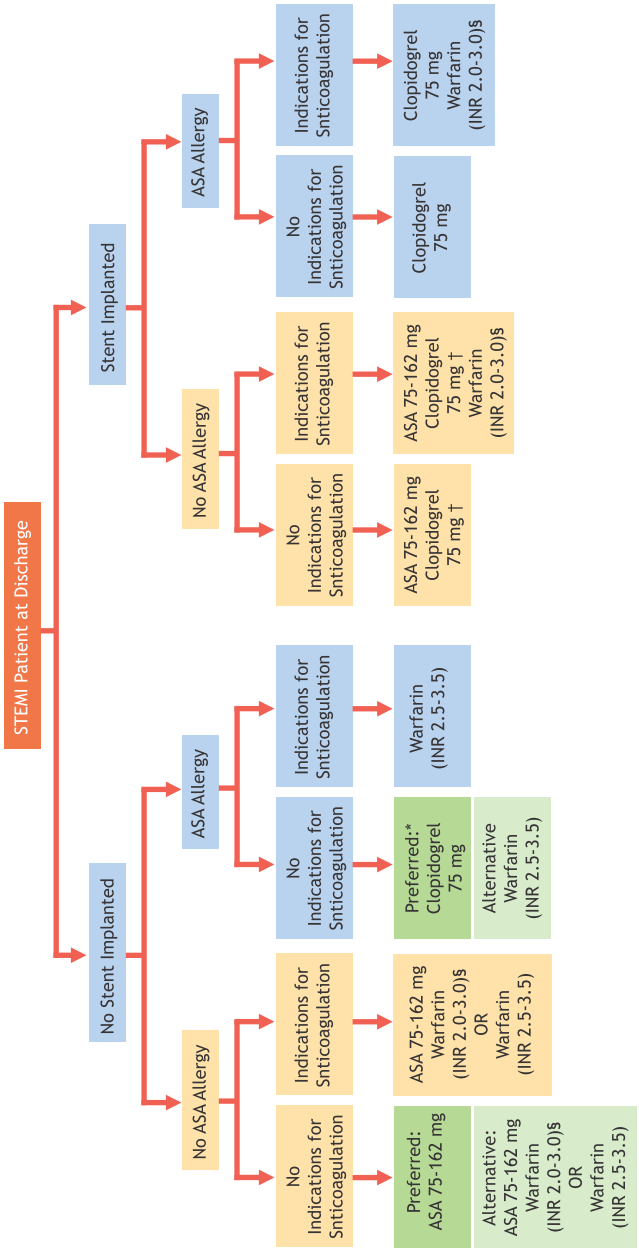
UFH vs LMWH

- For postoperative orthopedic surgery patients, the use of LMWH over UFH (Grade A) is recommended.

Bovine vs porcine UFH

- For the treatment of patients with thrombosis, the use of bovine UFH, in comparison with porcine UFH or LMWH (Grade A) is not recommended.
- For patients undergoing cardiac surgery, the use of porcine UFH for intraoperative anticoagulation, in comparison with bovine UFH (Grade A) is recommended.

Annexure 1


STEMI Patient at Discharge
Stent Implanted
ASA Allergy
Indications for Snticoagulation
Clopidogrel 75 mg Warfarin (INR 2.0-3.0)§
No Indications for Snticoagulation
Clopidogrel 75 mg
No ASA Allergy
Indications for Snticoagulation
ASA 75-162 mg Clopidogrel 75 mg † Warfarin (INR 2.0-3.0)§
No Indications for Snticoagulation
ASA 75-162 mg Clopidogrel 75 mg †
No Stent Implanted
ASA Allergy
Indications for Snticoagulation
Warfarin (INR 2.5-3.5)
No Indications for Snticoagulation
Preferred:* Clopidogrel 75 mg
Alternative Warfarin (INR 2.5-3.5)
No ASA Allergy
Indications for Snticoagulation
ASA 75-162 mg Warfarin (INR 2.0-3.0)§ OR Warfarin (INR 2.5-3.5)
No Indications for Snticoagulation
Preferred: ASA 75-162 mg
Alternative: ASA 75-162 mg Warfarin (INR 2.0-3.0)§ OR Warfarin (INR 2.5-3.5)