

Guidelines for  
**Antithrombotic Therapy**  
in the Management of  
Acute Coronary Syndrome  
and Venous Thromboembolism  
in Health Systems

Developed by ASHP Advantage



Supported by an educational grant  
from sanofi-aventis U.S. and the  
Bristol-Myers Squibb/Sanofi  
Pharmaceuticals Partnership



## EXECUTIVE SUMMARY

Acute coronary syndrome (ACS) and venous thromboembolism (VTE) represent a serious public health threat. Patients with ACS manifest non-ST-segment elevation myocardial infarction, unstable angina, or ST-segment elevation myocardial infarction, and VTE comprises deep vein thrombosis, pulmonary embolism, or both. Antithrombotic therapies play an important role in the management of ACS and VTE. These therapies include antiplatelet agents (aspirin, the thienopyridine clopidogrel, and the platelet glycoprotein IIb/IIIa inhibitors abciximab, eptifibatid, and tirofiban) and anticoagulants (unfractionated heparin; the low molecular weight heparin products enoxaparin, dalteparin, and tinzaparin; the activated factor X inhibitor fondaparinux, the direct thrombin inhibitor bivalirudin; and the vitamin K antagonist warfarin). Antithrombotic therapies often are not used appropriately with less than optimal outcomes in patients with ACS or VTE despite the availability of evidence-based guidelines for the use of these therapies in the management of ACS and VTE. This discussion guide addresses guidelines for the proper use of antithrombotic agents in the management of ACS and VTE.

Coronary heart disease (CHD), acute coronary syndrome (non-ST-segment elevation myocardial infarction [NSTEMI], unstable angina [UA], and ST-segment elevation myocardial infarction [STEMI]), and venous thromboembolism (deep vein thrombosis, pulmonary embolism, or both) are common and costly causes of morbidity and mortality in the United States. In 2006 (the most recent year for which statistics are available), more than 1.3 million Americans were hospitalized for acute coronary syndrome (ACS).<sup>1</sup> The estimated direct medical costs and indirect costs for lost productivity, morbidity, and mortality from CHD in the United States are expected to exceed \$165 billion in 2009.<sup>1</sup>

Each year there are more than 200,000 new cases of venous thromboembolism (VTE) in the United States.<sup>1</sup> Thirty percent of these patients die within 30 days, and approximately 30% experience recurrence of VTE within a 10-year period.<sup>1</sup> The annual costs of treating VTE in the United States may amount to \$1.5 billion.<sup>2</sup>

Antithrombotic drugs (anticoagulants with or without antiplatelet drugs) play an important role in the management of ACS and VTE. Evidence-based guidelines for the management of ACS and prevention and treatment of VTE that address antithrombotic therapies are available from various authoritative sources, including the American College of Cardiology (ACC), American Heart Association (AHA), and American College of Chest Physicians (ACCP).<sup>3-8</sup> These guidelines reflect recently published results of studies comparing therapeutic regimens involving antithrombotic agents. Adherence to guidelines for the management of ACS and prevention of VTE often is less than optimal.<sup>9,10</sup> This discussion guide was developed to describe the ACC/AHA and ACCP guidelines pertaining to the use of antithrombotic agents for the management of NSTEMI, UA, and STEMI and the prevention and treatment of VTE.

# Guidelines for **Antithrombotic Therapy** in the Management of Acute Coronary Syndrome and Venous Thromboembolism in Health Systems

## Guidelines for Managing NSTEMI and UA

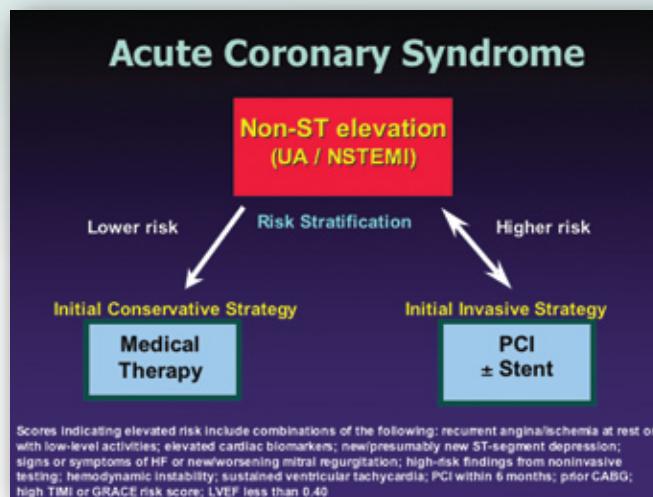
In 2007, ACC and AHA published evidence-based guidelines for the management of patients with NSTEMI or UA.<sup>3</sup> Guidelines released in 2008 by ACCP are fairly consistent with the 2007 ACC/AHA guidelines, although there are some noteworthy differences.<sup>4</sup> Please consult the guidelines for a detailed discussion of the clinical trial results that are the basis for the recommendations.

Antiplatelet and anticoagulant therapy recommendations in the ACC/AHA and ACCP guidelines depend on whether a conservative (i.e., noninvasive) approach or an invasive strategy (i.e., percutaneous coronary intervention [PCI] with possible angioplasty or coronary artery bypass graft [CABG] surgery) is planned (Figure 1).

### Antiplatelet Therapy

The ACC/AHA recommendations are classified based on the benefit, risk, and level of evidence, with class I recommendations reflecting the highest benefit-to-risk ratio.<sup>3</sup> The 2007 ACC/AHA class I recommendations for antiplatelet therapy in patients with NSTEMI or UA are listed in Table 1.<sup>3</sup> Immediate administration of a single 162- to 325-mg dose of non-enteric aspirin and addition of a 300- to 600-mg loading dose of the thienopyridine clopidogrel are recommended for all patients, regardless of whether an invasive or noninvasive strategy is chosen. Clopidogrel may be used instead of aspirin for patients who cannot take aspirin because of hypersensitivity or gastrointestinal (GI) intolerance.<sup>3</sup> Patients with a history of GI bleeding should receive drugs to minimize the risk of recurrent GI bleeding (e.g., proton pump inhibitors) when receiving aspirin, clopidogrel, or both.<sup>3</sup> Clopidogrel should be withheld for at least 5 days before elective CABG.<sup>3,4</sup>

In patients with NSTEMI or UA for whom a conservative approach is chosen, it may be reasonable to add a platelet glycoprotein (GP) IIb/IIIa inhibitor (eptifibatide or tirofiban) to aspirin and clopidogrel, especially in patients with recurrent ischemic discomfort with clopi-



**Figure 1. Management of Non-ST-Segment Elevation Myocardial Infarction and Unstable Angina**

dogrel, aspirin, and anticoagulants.<sup>3,4</sup> However, the GP IIb/IIIa inhibitor abciximab should be avoided in these patients.

In patients with NSTEMI or UA for whom an initial invasive strategy is chosen, upstream administration of a GP IIb/IIIa inhibitor with or instead of clopidogrel may be considered before angiography and PCI.<sup>3</sup> If appreciable delays in angiography and PCI are likely, eptifibatide or tirofiban is preferred over abciximab.<sup>3</sup> Upstream use of the GP IIb/IIIa inhibitor may be omitted if the direct thrombin inhibitor bivalirudin was used as the anticoagulant and at least 300 mg of clopidogrel was administered at least 6 hours prior to PCI.<sup>3</sup>

Patients undergoing PCI should receive a 600-mg loading dose of clopidogrel in combination with a GP IIb/IIIa inhibitor, and the clopidogrel loading dose should be given at least 2 hours prior to PCI.<sup>3,4</sup> ACCP guidelines include a recommendation against use of tirofiban instead of abciximab in patients undergoing PCI without upstream GP IIb/IIIa inhibitor therapy.<sup>4</sup>

According to ACC/AHA, patients undergoing bare-metal stent (BMS) placement should receive high-dose

TABLE 1

### ACC/AHA Class I Recommendations for Antiplatelet Therapy in Patients with NSTEMI or UA<sup>3</sup>

- Give a single 162- to 325-mg dose of non-enteric aspirin immediately
- Continue aspirin 162–325 mg/day for:
  - BMS: 1 month, then 75–162 mg/day indefinitely
  - SES: 3 months, then 75–162 mg/day indefinitely
  - PES: 6 months, then 75–162 mg/day indefinitely
- May use clopidogrel instead of aspirin for patients who cannot take aspirin
- If conservative (noninvasive) approach planned, add clopidogrel (300- to 600-mg loading dose) to aspirin as soon as possible and continue 75 mg/day for ≥1 month and ideally up to 1 year
- If PCI planned, start clopidogrel (300–600 mg as a loading dose followed by 75 mg/day) and aspirin (162–325 mg/day) before PCI and continue for:
  - BMS: ≥1 month and ideally up to 1 year (with aspirin reduced to 75–162 mg/day after 1 month)
  - DES: ≥1 year (with aspirin reduced to 75–162 mg/day after 3 months for SES and 6 months for PES)

ACC = American College of Cardiology; AHA = American Heart Association; BMS = bare metal stent; DES = drug-eluting stent; NSTEMI = non-ST elevation myocardial infarction; PCI = percutaneous coronary intervention; PES = paclitaxel-eluting stent; SES = sirolimus-eluting stent; UA = unstable angina

aspirin (162–325 mg/day) for at least 1 month, followed by 75–162 mg/day indefinitely.<sup>3</sup> Use of clopidogrel 75 mg/day for at least 1 month and ideally up to 12 months also is recommended for these patients.<sup>3</sup> ACCP guidelines call for low-dose aspirin (75–100 mg/day) and clopidogrel 75 mg/day for 12 months in patients with BMS placement.<sup>4</sup>

ACC/AHA guidelines recommend high-dose aspirin therapy for 3 months in patients receiving a sirolimus-eluting stent (SES) and 6 months for patients receiving a paclitaxel-eluting stent (PES), followed by 75–162 mg/day indefinitely regardless of type of drug-eluting stent (DES).<sup>3</sup> Clopidogrel 75 mg/day should be given to patients with a DES for at least 1 year in the absence of bleeding or tolerability issues.<sup>3,4</sup> ACCP guidelines call for low-dose aspirin (75–100 mg/day) and clopidogrel 75 mg/day for at least 12 months in patients with a DES.<sup>4</sup> Dual antiplatelet therapy may be continued beyond 1 year (i.e., indefinitely) in patients with a DES if no bleeding or tolerability issues arise, according to ACCP.<sup>11</sup>

### Anticoagulant Therapy

According to ACC/AHA guidelines, anticoagulant therapy should be added to antiplatelet therapy as soon as possible after presentation.<sup>3</sup> ACCP guidelines recommend the use of anticoagulation (unfractionated heparin [UFH], low molecular weight heparin [LMWH], bivalirudin, or the activated factor X inhibitor fondaparinux) over no anticoagulation in patients with NSTEMI or UA.<sup>4</sup> Dosing information for LMWH, fondaparinux, and bivalirudin in patients with NSTEMI or UA is provided in Table 2.

If a conservative strategy is chosen in a patient with NSTEMI or UA, subcutaneous (s.c.) enoxaparin or intravenous (i.v.) UFH is recommended by ACC and AHA (Table 3), with fondaparinux as an alternative that is preferred for patients at high risk for bleeding.<sup>3</sup> Enoxaparin or fondaparinux is preferred over UFH, unless CABG is planned within 24 hours.

TABLE 2

### Dosing of LMWH, Fondaparinux, and Bivalirudin in Patients with NSTEMI or UA<sup>12–14</sup>

- Enoxaparin 1 mg/kg s.c. every 12 hr
- Dalteparin 120 units/kg (not to exceed 10,000 units) s.c. every 12 hr
- Fondaparinux 2.5 mg s.c. once daily
- Bivalirudin 0.75 mg/kg as an i.v. bolus followed by 1.75 mg/kg/hr i.v.

i.v. = intravenous; LMWH = low molecular weight heparin; NSTEMI = non-ST-segment elevation myocardial infarction; s.c. = subcutaneous; UA = unstable angina

TABLE 3

### ACC/AHA Recommendations for Anticoagulant Therapy in Patients with NSTEMI or UA<sup>3</sup>

#### Conservative (noninvasive) treatment strategy

- Enoxaparin or i.v. UFH
- Fondaparinux (preferred in patients at high risk for bleeding)
- Enoxaparin and fondaparinux preferred over UFH unless CABG planned within 24 hr

#### Invasive treatment strategy

- Enoxaparin or i.v. UFH
- Fondaparinux or bivalirudin as alternatives

ACC = American College of Cardiology; AHA = American Heart Association; CABG = coronary artery bypass grafting; i.v. = intravenous; NSTEMI = non-ST elevation myocardial infarction; UA = unstable angina; UFH = unfractionated heparin

ACCP guidelines recommend fondaparinux over enoxaparin for patients with NSTEMI or UA in whom a conservative strategy is chosen.<sup>4</sup> In patients receiving fondaparinux who later require PCI, additional i.v. bolus doses of UFH 50–60 units/kg and fondaparinux 2.5–5 mg are recommended by ACCP at the time of the procedure.<sup>4</sup>

ACCP guidelines also recommend LMWH over UFH in patients for whom a conservative strategy is chosen.<sup>4</sup> Continuation of LMWH is recommended if such patients later require PCI. In patients receiving enoxaparin who require PCI, use of an additional 0.3-mg/kg enoxaparin dose is recommended at the time of PCI if 8–12 hours have elapsed since the last enoxaparin dose, but no additional enoxaparin dose is needed at the time of PCI if less than 8 hours have elapsed since the last dose.<sup>4</sup>

In patients with NSTEMI or UA for whom an invasive strategy is chosen, ACC/AHA recommendations for anticoagulant therapy include s.c. enoxaparin or i.v. UFH, with the bivalirudin or fondaparinux as alternatives (Table 3).<sup>3</sup> ACCP guidelines recommend the use of UFH (with a GP IIb/IIIa inhibitor) over LMWH or fondaparinux.<sup>4</sup> However, if LMWH was used upstream, ACCP recommends continuation of LMWH during PCI instead of switching to UFH. In moderate- to high-risk patients, use of bivalirudin is preferred over UFH by ACCP if clopidogrel was given at least 6 hours prior to PCI.<sup>4</sup>

When UFH is used, ACC/AHA recommends dosing to maintain an activated partial thromboplastin time (aPTT) 1.5 to 2.0 times the control value (50–70 seconds).<sup>3</sup> ACCP guidelines recommend the use of weight-based dosing of UFH with a target aPTT of 50–70 seconds.<sup>4</sup> When LMWH is used, ACCP guidelines recommend against routine monitoring for the anticoagulant effect.<sup>4</sup>

## Guidelines for Managing STEMI

Patients with STEMI require prompt reperfusion to minimize myocardial damage, and reperfusion may be accomplished through fibrinolytic therapy or primary PCI. Antiplatelet and anticoagulation therapies play important roles in both strategies.

### Antiplatelet Therapy

Guidelines for antiplatelet therapy in patients with STEMI released by ACC/AHA and ACCP are generally consistent. After an initial chewable aspirin dose of 160–325 mg, aspirin 75–162 mg/day should be given indefinitely, although patients undergoing primary PCI

TABLE 4

### Antiplatelet Therapy in Patients with STEMI<sup>5,6,15–18</sup>

- Initial aspirin dose: 160–325 mg
- Subsequent aspirin doses: 75–162 mg/day indefinitely
- After PCI and stent placement in patients without allergy or increased risk of bleeding, give aspirin 162–325 mg/day for:
  - ≥1 month with BMS
  - ≥3 months with SES
  - ≥6 months with PES
- Add clopidogrel 75 mg/day to aspirin regardless of reperfusion strategy
  - Discontinue clopidogrel for ≥5 days prior to CABG surgery
  - Patients receiving fibrinolytic therapy
  - Age >75 years: give 300-mg clopidogrel loading dose followed by 75 mg/day
  - Age >75 years: give clopidogrel 75 mg/day without a loading dose
  - Continue clopidogrel for 28 days or up to 1 year
- Patients undergoing primary PCI
  - Give clopidogrel 300 mg followed by 75 mg/day
  - Continue clopidogrel for ≥4 weeks for BMS
  - Continue clopidogrel for 12 months or indefinitely for DES
- Patients with STEMI (with or without stent placement) and indication for warfarin (e.g., chronic atrial fibrillation or flutter): may use triple antithrombotic therapy
  - Warfarin with a target INR of 2.0–2.5
  - Low-dose aspirin 75–81 mg/day
  - Clopidogrel 75 mg/day

BMS = bare metal stent; CABG = coronary artery bypass graft; DES = drug-eluting stent; INR = international normalized ratio; PCI = percutaneous coronary intervention; PES = paclitaxel-eluting stent; SES = sirolimus-eluting stent; STEMI = ST-segment elevation myocardial infarction

should receive larger doses for 1–6 months, depending on the type of stent implanted (Table 4).<sup>5,6</sup> In patients without allergy or increased risk of bleeding, high-dose aspirin 162–325 mg/day should be given for at least 1 month after BMS placement, 3 months after SES placement, and 6 months after PES placement, followed by 75–162 mg/day indefinitely.<sup>16</sup>

Clopidogrel should be added to aspirin regardless of the reperfusion strategy. In patients receiving fibrinolytic therapy, a 300-mg clopidogrel loading dose followed by 75 mg/day is recommended for patients 75 years of age or younger, and clopidogrel 75 mg/day without a loading dose is recommended for patients more than 75 years of age.<sup>6</sup> Clopidogrel therapy should be continued for 28 days or up to 1 year.<sup>6</sup>

In patients undergoing primary PCI, use of clopidogrel 300 mg as a loading dose followed by 75 mg/day is recommended for at least 4 weeks for patients with BMS placement or 12 months or indefinitely for patients with DES placement, according to ACCP.<sup>6</sup> Guidelines from ACC/AHA call for consideration of long-term therapy for 1 year regardless of reperfusion strategy.<sup>5</sup> Clopidogrel should be discontinued at least 5 days before CABG surgery.<sup>5,6</sup>

Patients with STEMI (with or without stent placement) and an indication for warfarin (e.g., low ejection fraction and substantial akinesis on the echocardiogram, chronic atrial fibrillation or flutter, presence of a mechanical prosthetic heart valve, recent VTE, presence of a left ventricular thrombus) may receive triple antithrombotic therapy. This therapy comprises warfarin with a target international normalized ratio (INR) of 2.0–2.5, low-dose aspirin 75–81 mg/day, and clopidogrel 75 mg/day.<sup>5,15,17,18</sup>

### Anticoagulant Therapy

Guidelines for anticoagulant therapy in patients with STEMI released by ACC/AHA and ACCP are generally consistent. The use of i.v. UFH, enoxaparin, or fondaparinux is recommended for patients receiving fibrinolytic therapy, with some caveats specified in the ACCP guidelines (Table 5).<sup>5,6</sup> ACCP guidelines for patients with STEMI who receive fibrinolytic therapy call for the use of UFH 60 units/kg (maximum 4000 units) as an i.v. bolus followed by 12 units/kg/hr (maximum 1000 units/hr) i.v. for 48 hours with a target aPTT of 50–70 seconds.<sup>6</sup> In patients with preserved renal function (serum creatinine <2.5 mg/dL in men and <2.0 mg/dL in women), a preference for the use of enoxaparin over UFH for up to 8 days is recommended.<sup>6</sup> Fondaparinux is considered an alternative to UFH in patients with preserved renal function. Bivalirudin is not an option for patients receiving fibrinolytic therapy because it has not been studied in this patient population. The ACCP guidelines include a specific recommendation against the use of bivalirudin as an alternative to UFH in patients treated with streptokinase.<sup>6</sup>

ACCP guidelines for patients with STEMI who undergo primary PCI (Table 6) call for the use of i.v. UFH 50–70 units/kg if the patient is receiving a GP IIb/IIIa inhibitor and 60–100 units/kg if the patient is not receiving a GP IIb/IIIa inhibitor.<sup>6</sup> A recommendation against use of fondaparinux in patients undergoing PCI is included in the ACCP guidelines.<sup>6</sup> Guidelines from ACC/AHA recommended avoidance of fondaparinux as the sole anticoagulant during PCI because of risk of catheter-related

TABLE 5

### Anticoagulant Therapy in Patients with STEMI Who Receive Fibrinolytic Therapy<sup>6,19</sup>

- **UFH:** 60 units/kg (maximum 4000 units) as an i.v. bolus followed by 12 units/kg/hr (maximum 1000 units/hr) i.v. with aPTT 50–70 sec for 48 hr
- **Enoxaparin:** started between 15 min before and 30 min after the start of fibrinolytic therapy
  - Normal renal function or mild or moderate renal impairment (CrCl ≥30 mL/min)
    - Age <75 yr: 30 mg as an i.v. bolus, followed by 1 mg/kg s.c. every 12 hr (maximum 100 mg for first two doses) for up to 8 days
    - Age ≥75 yr: 0.75 mg/kg s.c. every 12 hr (maximum 100 mg for first two doses) for up to 8 days (i.e., without an i.v. bolus)
  - Severe renal impairment (CrCl <30 mL/min)
    - Age <75 yr: 30 mg as an i.v. bolus, followed by 1 mg/kg s.c. every 24 hr (maximum 100 mg for first two doses) for up to 8 days
    - Age ≥75 yr: 1 mg/kg s.c. every 24 hr (maximum 75 mg for first two doses) for up to 8 days (i.e., without an i.v. bolus)
- **Fondaparinux:** 2.5 mg i.v. followed by 2.5 mg/day s.c. for 9 days

aPTT = activated partial thromboplastin time; CrCl = creatinine clearance; i.v. = intravenous; s.c. = subcutaneous; STEMI = ST-segment elevation myocardial infarction

TABLE 6

### Anticoagulant Therapy in Patients with STEMI Who Undergo Primary PCI<sup>6,14</sup>

- **UFH:** 50–70 units/kg i.v. if the patient is receiving a GP IIb/IIIa inhibitor and 60–100 units/kg i.v. if the patient is not receiving a GP IIb/IIIa inhibitor
- **Enoxaparin:** give additional 0.3-mg/kg i.v. bolus if >8 hr have elapsed since last dose (no additional dose needed if <8 hr elapse between last dose and PCI)
- **Abciximab:** 0.25 mg/kg as an i.v. bolus, followed by 0.125 mcg/kg/min (maximum 10 mcg/min) for 12 hr
- **Eptifibatide:** two 180-mcg i.v. boluses 10 minutes apart, followed by 2.0 mcg/kg/min i.v. for 12–24 hr
- **Tirofiban:** 25 mcg/kg as an i.v. bolus, followed by 0.15 mcg/kg/min for 24 hr
- **Bivalirudin:** 0.75 mg/kg as an i.v. bolus followed by 1.75 mg/kg/hr i.v. for the duration of the procedure

GP = glycoprotein; i.v. = intravenous; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction

thrombosis.<sup>5</sup> No recommendation is made for the use of enoxaparin or bivalirudin in patients undergoing PCI in the ACCP guidelines, although the ACC/AHA guidelines include a class I recommendation for enoxaparin.<sup>5</sup> The ACCP guidelines call for the use of a GP IIb/IIIa inhibitor, with a Grade 1B recommendation (i.e., a strong recommendation based on moderate-quality evidence) for abciximab but no grade recommendation for eptifibatide or tirofiban.<sup>6</sup> By contrast, ACC/AHA guidelines published in 2004 recommend the use of abciximab (class IIa) or eptifibatide or tirofiban (class IIb, with a smaller treatment effect) in patients undergoing PCI.<sup>15</sup>

## Prevention of VTE

Updated guidelines for the prevention of VTE were released by ACCP in 2008.<sup>7</sup> The strategy for preventing VTE recommended by ACCP depends on the level of risk for DVT without prophylaxis (Table 7).<sup>7</sup> No specific thromboprophylaxis is required for patients undergoing minor surgery who are ambulatory. Early and aggressive ambulation is recommended for medical patients who are fully ambulatory. The risk for DVT in both types of patients is low (<10%) without thromboprophylaxis.

The risk for DVT without thromboprophylaxis in most general, open gynecology or urologic surgery patients and medical patients who are on bed rest or acutely ill is moderate (10% to 40%).<sup>7</sup> Therefore, LMWH (at recommended dosages), low-dose UFH (5000 units s.c.) two or three times daily (usually three times daily), or fondaparinux is recommended in these patients. Dosing information is provided for LMWH and fondaparinux in Table 8. Mechanical thromboprophylaxis using intermittent pneumatic compression (IPC) (optional Figure 2), a venous foot pump (VFP), and/or graduated compression stockings (GCS) is recommended instead of anticoagulant therapy for patients who are at moderate risk for VTE and at high risk for bleeding.

The risk for VTE in patients undergoing hip or knee arthroplasty or hip fracture surgery and patients with major trauma or spinal cord injury is high (40% to 80%) unless they receive thromboprophylaxis.<sup>7</sup> High-risk patients should receive LMWH (at recommended dosages), fondaparinux, or an oral vitamin K antagonist (VKA) with an INR of 2–3, unless the patient also is at high risk for bleeding. Patients at high risk for VTE and bleeding should receive mechanical thromboprophylaxis using IPC, VFP, and/or GCS instead of anticoagulant therapy.

TABLE 7

### ACCP Recommendations for Thromboprophylactic Strategy Based on Risk for VTE<sup>7</sup>

Recommended Level of Risk for VTE	Thromboprophylactic Strategy
<b>Low Risk</b>	
■ Minor surgery in mobile patients	No specific prophylaxis
■ Medical patients who are fully mobile	Early and aggressive ambulation
<b>Moderate Risk</b>	
■ Most general, open gynecology or urologic surgery patients	LMWH (at recommended dosages), LDUH two or three times daily, fondaparinux
■ Medical patients, bed rest or sick	LMWH (at recommended dosages), LDUH two or three times daily, fondaparinux
■ Moderate VTE risk plus high bleeding risk	Mechanical thromboprophylaxis (IPC or VFP and/or GCS)
<b>High Risk</b>	
■ Hip or knee arthroplasty, hip fracture surgery	LMWH (at recommended dosages), fondaparinux, oral VKA (INR 2–3)
■ Major trauma, spinal cord injury	LMWH (at recommended dosages), fondaparinux, oral VKA (INR 2–3)
■ High VTE risk plus high bleeding risk	Mechanical thromboprophylaxis (IPC or VFP and/or GCS)

ACCP = American College of Chest Physicians; GCS = graduated compression stockings; INR = international normalized ratio; IPC = intermittent pneumatic compression; LDUH = low-dose unfractionated heparin; LMWH = low molecular weight heparin; VFP = venous foot pump; VKA = vitamin K antagonist; VTE = venous thromboembolism



Figure 2. Intermittent Pneumatic Compression for Prevention of Venous Thromboembolism in the Lower Extremities

TABLE 8  
**VTE Prophylactic Dosing of LMWH and Fondaparinux<sup>13, 19-22</sup>**

Type of Patient	Enoxaparin	Dalteparin	Tinzaparin	Fondaparinux
<b>Hip Fracture Surgery</b>	30 mg s.c. every 12 hr starting 12–24 hr after surgery	<sup>a</sup>	<sup>a</sup>	2.5 mg s.c. once daily starting 6–8 hr after surgery
<b>Hip Replacement Surgery</b>	30 mg s.c. every 12 hr starting 12–24 hr after surgery or 40 mg s.c. once daily starting 10–12 hr prior to surgery	2500 units s.c. 4–8 hr after surgery, then 5000 units s.c. every 24 hr OR 5000 units s.c. 10–14 hr before and 4–8 hr after surgery, then once daily thereafter	75 units/kg s.c. every 24 hr starting the evening prior to surgery or 12–24 hr after surgery OR 4500 units s.c. every 24 hr starting 12 hr prior to surgery <sup>a</sup>	2.5 mg s.c. once daily starting 6–8 hr after surgery
<b>Knee Replacement Surgery</b>	30 mg s.c. every 12 hr starting 12–24 hr after surgery	2500 units s.c. 6–8 hr after surgery, then 5000 units s.c. every 24 hr <sup>a</sup>	75 units/kg s.c. every 24 hr starting the evening prior to surgery or 12–24 hr after surgery <sup>a</sup>	2.5 mg s.c. once daily starting 6–8 hr after surgery
<b>Abdominal Surgery</b>	40 mg s.c. once daily starting 1–2 hr prior to surgery	2500 units s.c. 1–2 hr prior to surgery and once daily thereafter OR in patients with malignancy, 2500 units s.c. 1–2 hr prior to and 12 hr after surgery, then 5000 units s.c. every 24 hr	3500 units s.c. every 24 hr starting 1–2 hr prior to surgery <sup>a</sup>	2.5 mg s.c. once daily starting 6–8 hr after surgery
<b>Acute Medical Illness</b>	40 mg s.c. once daily	5000 units s.c. every 24 hr	<sup>a</sup>	2.5 mg s.c. once daily <sup>a</sup>

<sup>a</sup> Indication not approved by FDA

FDA = Food and Drug Administration; LMWH = low molecular weight heparin; s.c. = subcutaneous; VTE = venous thromboembolism

Cancer patients undergoing surgery or bedridden with acute medical illness should receive routine thromboprophylaxis (i.e., what is customarily used based on the type of surgery or for patients with acute medical illness).<sup>7</sup> In cancer patients with indwelling central venous catheters, ACCP recommends against using prophylactic doses of LMWH or minidose warfarin (i.e., 1 mg/day) for the prevention of catheter-related thrombosis.<sup>7</sup> The routine use of thromboprophylaxis for primary prevention of VTE is not recommended for cancer patients receiving chemotherapy or hormonal therapy. The routine use of primary thromboprophylaxis for improvement of survival in cancer patients also is not recommended.

In trauma patients, LMWH is preferred unless it is contraindicated because of active bleeding or a

high risk of clinically important bleeding.<sup>7</sup> The use of routine screening Doppler ultrasonography (DUS) for asymptomatic DVT and use of inferior vena cava filters are not recommended for trauma patients.

In patients undergoing inpatient bariatric surgery, LMWH, low-dose UFH (LDUH) three times daily, or fondaparinux alone or with IPC is recommended by ACCP.<sup>7</sup> The doses of LMWH and LDUH used for these obese patients should be larger than those used for nonobese patients. Weight-based prophylactic doses of LMWH are recommended for obese patients.<sup>23</sup>

In patients undergoing major orthopedic surgery, LMWH may be initiated preoperatively or postoperatively.<sup>7</sup> If fondaparinux is used instead, it should be initiated 6 to 8 hours after surgery or the next day. Routine use of screening DUS before discharge is not

recommended in asymptomatic patients after major orthopedic surgery. Patients undergoing total hip or knee replacement or hip fracture surgery should receive thromboprophylaxis for at least 10 days and up to 35 days.<sup>7</sup>

Long-distance travelers taking flights lasting more than 8 hours should avoid constrictive clothing around the lower extremities and waist, maintain adequate hydration, and contract their calf muscles frequently during the flight.<sup>7</sup> The use of GCS during travel or a single LMWH dose prior to departure may be considered for long-distance travelers who are at high risk for VTE. Aspirin alone provides inadequate thromboprophylaxis for long-distance travelers and surgical and medical patients whose risk for DVT is low, moderate, or high.<sup>7</sup>

## Treatment of VTE

Therapeutic options for patients with objectively confirmed DVT or PE include s.c. LMWH, monitored i.v. or s.c. UFH, unmonitored weight-based s.c. UFH, and s.c. fondaparinux plus the oral VKA warfarin (Table 9).<sup>8</sup> Treatment with anticoagulants may be initiated in patients with a high clinical suspicion of VTE before a formal diagnosis is made. Treatment of acute DVT should be initiated with s.c. LMWH once or twice daily on an outpatient basis if possible or s.c. fondaparinux once daily. In patients with acute VTE and severe renal impairment (creatinine clearance <30 mL/min), UFH is preferred over LMWH and fondaparinux. In patients with acute VTE who cannot receive anticoagulant therapy because of a risk of bleeding, inferior vena cava filter placement (Figure 3) is recommended until the risk of bleeding resolves, at which time anticoagulant therapy should be provided.

Patients who are unexpectedly found to have asymptomatic VTE should be treated in a manner comparable to that for symptomatic VTE. Acute upper-extremity DVT should be treated in the same manner as lower-extremity DVT, with therapeutic doses of UFH, LMWH, or fondaparinux.

Treatment with a VKA should be initiated with LMWH, UFH, or fondaparinux therapy, and the LMWH, UFH, or fondaparinux should be continued for at least 5 days, until an INR of at least 2.0 has been achieved and maintained for at least 24 hours (i.e., the two therapies should overlap for at least 5 days).<sup>8</sup> ACCP guidelines discourage the use of pharmacogenetic testing to individualize initial VKA doses.<sup>25</sup> The VKA dose should be adjusted to maintain a target INR of 2.5 (range 2.0–3.0).<sup>8</sup> In patients receiving a stable VKA dose, INR monitor-

TABLE 9

## Anticoagulant Treatment of VTE<sup>8,13,19–22,24,25</sup>

### UFH

- Monitored i.v. or s.c. or unmonitored weight-based s.c. therapy (e.g., 333 units/kg s.c. as a loading dose followed by 250 units/kg s.c. every 12 hr)
- Preferred in severe renal failure (CrCl <30 mL/min)

### LMWH

- Facilitates outpatient treatment, early discharge
- Enoxaparin 1 mg/kg s.c. every 12 hr
- Dalteparin 100 units/kg s.c. twice daily or 200 units/kg s.c. once daily (for extended treatment of VTE in cancer patients, 200 units/kg not to exceed 18,000 units s.c. once daily for 1 month, then 150 units/kg not to exceed 18,000 units s.c. once daily s.c. for 5 months)
- Tinzaparin 175 units/kg s.c. once daily
- Patients with severe renal impairment (CrCl <30 mL/min)
  - Use enoxaparin 1 mg/kg s.c. once daily instead of standard 1 mg/kg s.c. every 12 hr
  - Monitor anti-Xa levels during dalteparin therapy (target range 0.5–1.5 IU/mL)

### Fondaparinux

- Weight-based dosing: 5 mg for <50 kg, 7.5 mg for 50–100 kg, or 10 mg for >100 kg s.c. once daily

### Warfarin

- Start on same day as UFH, LMWH, or fondaparinux
- Discontinue UFH, LMWH, or fondaparinux after overlap of at least 5 days and when INR stable and >2.0
- Adjust dose to maintain target INR of 2.5 (range 2.0–3.0)
- In patients receiving stable dose, perform INR monitoring no less often than once every 4 weeks

CrCl = creatinine clearance; INR = international normalized ratio; i.v. = intravenous; LMWH = low molecular weight heparin; s.c. = subcutaneous; UFH = unfractionated heparin; VTE = venous thromboembolism

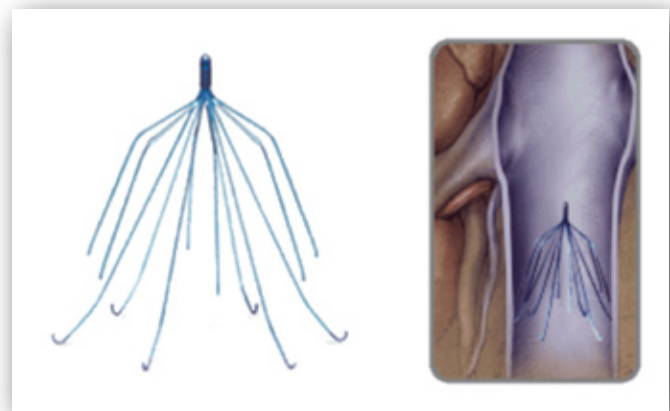


Figure 3. Inferior Vena Cava Filter

TABLE 10

## Duration of Anticoagulant Therapy in Patients with VTE<sup>8</sup>

- VTE with transient (reversible) cause: preference for 3 months over shorter periods
- Unprovoked VTE: recommendation for at least 3 months, with evaluation of the risks and benefits of long-term therapy after 3 months
- Patients with a first unprovoked proximal DVT or PE and low risk of bleeding: long-term therapy recommended when consistent with patient preference
- Patients with first isolated distal DVT that is unprovoked: 3 months of therapy usually suffices
- Patients with second unprovoked DVT: long-term therapy recommended
- Patients with VTE and cancer: 3–6 months of treatment with LMWH, followed by treatment with LMWH or VKA indefinitely or until cancer resolves

DVT = deep vein thrombosis; LMWH = low molecular weight heparin; PE = pulmonary embolism; VKA = vitamin K antagonist; VTE = venous thromboembolism

ing should be performed no less often than once every 4 weeks.<sup>25</sup> In patients receiving long-term warfarin therapy with an unstable INR, low-dose oral vitamin K supplementation (100–200 mg/day) is suggested.<sup>25</sup>

Continuation of VKA therapy for 3 months is preferred over a shorter duration of therapy in patients with VTE caused by a transient (reversible) risk factor (Table 10).<sup>8</sup> Patients with VTE and cancer should receive 3–6 months of LMWH therapy, followed by LMWH or VKA therapy for as long as the cancer is active.<sup>8</sup>

If VTE was unprovoked, VKA therapy should be continued for at least 3 months, with indefinite continuation of therapy considered based on an evaluation of the risks and benefits of such therapy.<sup>8</sup> Indefinite anticoagulant therapy is recommended for patients with a first unprovoked proximal DVT or PE and a low risk of bleeding (if such therapy is consistent with patient preference) and most patients with a second unprovoked DVT. Three months of anticoagulant therapy usually suffices for patients with a first isolated distal DVT that is unprovoked. In patients with unprovoked VTE and a preference for less frequent INR monitoring than at least once every 4 weeks, low-intensity maintenance therapy with an INR of 1.5–1.9 may be used (after 3 months of conventional anticoagulation with an INR of 2.0–3.0).<sup>8</sup>

In patients with symptomatic proximal DVT, the use of GCS is recommended beginning as soon as is feasible after starting anticoagulant therapy and continuing for at least 2 years.<sup>8</sup> In patients with spontaneous superficial vein thrombosis, the use of prophylactic or intermediate doses of LMWH or intermediate doses of UFH is recommended, with therapy continued for at least 4 weeks.<sup>8</sup> Alternatively, LMWH or UFH therapy may be switched to a VKA with an overlap of therapy for at least 5 days, using a target INR of 2.0–3.0.

## Conclusion

Antithrombotic therapies play an important role in the management of ACS and VTE. Comprehensive evidence-based guidelines for the use of these therapies provide guidance on the proper use of antithrombotic therapies to optimize patient outcomes.

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