LTC Information Series

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Dedicated To Long Term Care Medicine

Antithrombotic Therapy

in the Long Term Care Setting

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1. INTRODUCTION TO ANTITHROMBOTIC THERAPY IN THE LONG TERM CARE SETTING

Antithrombotic therapy represents the mainstay of treatment and preventive measures in patients with atherothrombotic diseases.[1] Both the incidence and prevalence of these diseases increase with age.[1-3] Patients residing in the long term care (LTC) setting are highly susceptible to atheroembolic events by reason of their age and general vulnerability.[4-6]

Although advances have occurred in the diagnosis and treatment of atherothrombotic diseases,[7,8] in the LTC setting, antithrombotic medications remain the principal treatment option. Clinical decisions are challenging in this setting because of the paucity of data specific to treatment of the frail elderly and the predisposition of this patient population to adverse drug reactions.[1]

This Information Tool Kit is intended to help practitioners optimally manage the use of antithrombotic therapies in elderly patients in the LTC setting. To the extent possible, this document draws on evidence from large, well-designed, randomized clinical trials; when such evidence does not exist, it presents suggested best practices based on the available literature and expert consensus. This Information Tool Kit focuses on issues related to atherothrombotic diseases that are addressed within the LTC facility. Procedures performed and care provided in the acute-care setting are beyond the scope of this document.

Categories of Antithrombotic Agents

Antithrombotic medications fall into several categories, differentiated by their primary mechanism of action.

Antiplatelet drugs (aspirin, clopidogrel, dipyridamole, GPIIb/IIIa-receptor antagonists, prasugrel, ticagrelor) affect arterial thrombosis associated with platelet aggregation.

Anticoagulant drugs affect venous thrombosis through several mechanisms: inhibition of both thrombin and factor Xa (heparin, low-molecular-weight heparins [LMWHs]); inhibition of factor Xa alone (fondaparinux, rivaroxaban); reduction of clotting-factor concentrations (warfarin, vitamin K antagonists); and inhibition of thrombin or factor IIa (argatroban injection, bivalirudin injection, dabigatran, lepirudin injection).[9,10] As this Information Tool Kit went to press, the factor Xa inhibitor apixaban awaited U. S. Food and Drug Administration (FDA) approval with an indication of atrial fibrillation.

The primary goal of antithrombotic therapy is to reduce the risk of blood clots (thrombi) and thromboemboli in patients who are at risk for such events, thereby reducing the incidence of stroke, myocardial infarction (MI), deep vein thrombosis (DVT), pulmonary embolism (PE), and other vascular events. Because antithrombotic therapies do not eliminate risk, some strokes and other serious vascular events will occur despite optimal treatment. When blood clots or thromboemboli occur, antithrombotic therapy should aim to maximize patient benefits and minimize therapy-related adverse drug events.

The availability of several newer antithrombotic agents with different mechanisms of action (LMWHs, factor Xa inhibitors, direct thrombin inhibitors) offers the practitioner a variety of options for prophylaxis and treatment of atherothrombotic conditions. Each agent has its merits in terms of safety and efficacy, as well as caveats to consider.

These agents may offer certain advantages over conventional therapy such as reduced nursing time, a reduced need for monitoring of the international normalized ratio, elimination of delays in obtaining lab results, and a potential improvement in the ability to achieve predictable anticoagulation.

Cardiovascular Disease in the Long Term Care Setting

Many patients residing in LTC facilities have been diagnosed with cardiovascular disease or have cardiovascular risk factors that place them at risk for ischemic events. Compared with the general population, patients who have a history of ischemic events are at increased risk for MI and stroke over the following 10 years.[11]

Those who have suffered an MI have a 5- to 7-fold increased risk of having another, potentially fatal MI and a 3- to 4-fold increased risk of having a transient ischemic attack (TIA) or stroke.[12] Those who have suffered a stroke have a 2- to 3-fold increased risk of MI, angina, and sudden cardiac death, and a 9-fold increased risk of a second stroke.[12] Those with peripheral arterial disease (PAD) have a 4-fold increased risk of suffering a fatal MI or other form of death related to coronary artery disease (CAD),[13] and a 2- to 3-fold increased risk of having a stroke or TIA.[12]

For these patients, arterial thrombosis—particularly atherothrombosis—is the main cause of MI, ischemic stroke, and acute peripheral vascular ischemia. Arterial thrombosis may occur in several vascular beds, including the cardiac chambers, cerebrovascular arteries, coronary arteries, and peripheral arterial vessels. Elderly patients often have coexisting cardiovascular disease in multiple vascular beds.[14] The risk of atherothrombosis can be reduced by controlling risk factors (e.g., diabetes, hyperlipidemia, hypertension, smoking) and by prescribing appropriate antithrombotic therapy.

Oral antiplatelet agents effectively reduce atherothrombotic events in patients who have CAD, PAD, or prior stroke or TIA. Anticoagulants can effectively reduce the risk of venous and arterial thromboembolic events. Despite the known effectiveness of drug therapy in reducing atherothrombotic events in patients at risk, however, opportunities for secondary prevention in the LTC setting often are missed.[15]

Venous Thromboembolism in the Long Term Care Setting

Venous thromboembolism (VTE), which comprises both DVT and PE, is particularly common in elderly people.[16-18] DVT generally is caused by hypercoagulability, intimal injury, and stasis. Both DVT and PE have numerous risk factors (Table 1.1), and the incidence of both conditions increases with age. Both sexes and all races are affected about equally. The condition is most commonly seen in patients who suffer trauma, undergo major surgery (particularly orthopedic surgery), have a condition that predisposes them to a hypercoagulable state (e.g., cancer), or are immobilized for prolonged periods.

DVT occurs most frequently in the veins of the lower extremities, although it also may occur in the pelvic veins, the upper-extremity veins, or the cerebral or retinal veins. DVT can result in postphlebitic syndrome, which is characterized by pain, swelling, and ulceration of the affected limb. PE occurs when a distal clot is dislodged, travels through the bloodstream, and causes an ischemic occlusion of part of the pulmonary arterial tree, with potentially fatal results.

Most patients in the LTC setting have at least two risk factors for VTE: advanced age and LTC facility confinement.[19] While the benefit of VTE prophylaxis for hos-

pitalized, medically ill patients is clear, it is unknown whether the principles of hospital-based VTE prophylaxis apply to LTC patients. When considering the appropriateness of VTE prophylaxis, it may be helpful to differentiate between recently admitted and long-stay patients.

Studies of long-stay LTC patients have shown an incidence of 1.3 to 1.6 events per 100 person-years of observation.[17,18] Somewhat counter-intuitively, immobility alone is not a powerful predictor of VTE in long-stay LTC patients.[17,18] One study showed that VTE risk decreases as the length of time an LTC patient is immobile increases.[20] Patients recently admitted to an LTC facility from the hospital have a much higher risk for acute VTE than do long-stay LTC patients.[19,20]

Patients admitted to an LTC facility following a nonsurgical hospital stay are 6 to 8 times as likely as LTC patients who have not been hospitalized to suffer DVT or PE. Patients admitted following a recent surgery are 22 times as likely as those who have not had surgery to develop a DVT.[19,20] Continuation of prophylaxis with LMWH for VTE following hospitalization is clearly beneficial for postoperative hip-fracture surgery patients. While a recent study of post-acute-care patients admitted to LTC facilities showed that a multimodal VTE prophylaxis initiative can reduce VTE,[21] no large-scale trials exist to guide the type or duration of anticoagulant therapy for LTC patients following hospital discharge.

A Prudent Management Strategy for Thromboembolic Disease in the Long Term Care Setting

The most appropriate strategy for managing thromboembolic disease depends on whether the objective is prevention or treatment and on whether the disease involves the venous or arterial circulation. Patients who are at high risk for thromboembolism may receive prophylactic doses of anticoagulant or antithrombotic agents to prevent the development or propagation of a clot. Patients with limb ischemia, MI, or stroke caused by acute thrombosis are appropriate candidates for urgent evaluation and medical or surgical intervention to restore blood flow.

The management of elderly patients who need antithrombotic therapy is challenging because advancing age increases both the risks and the potential benefits of such therapy. Table 1.2 describes a stepwise process for the prudent management of antithrombotic therapy in frail elderly patients. This approach complies with good geriatric care as well as with the intent of regulatory oversight to limit unnecessary medications. This medication management strategy includes documenting the diagnosis, potential benefits and risks, parameters for assessing treatment efficacy, duration of therapy, plans to reduce the risk of adverse effects, and methods of monitoring for potential adverse effects.

Principles of Clinical Decision-Making Related to Antithrombotic Therapy

Some patients who are treated with antithrombotic agents will suffer life-threatening side effects despite careful prescribing and monitoring. The clinical decision to prescribe antithrombotic therapy must therefore be considered carefully. It is prudent to discuss the benefits and burdens of treatment and nontreatment as fully and frankly as possible with the patient and family or legally authorized representative, reach a shared decision, and document both the discussion and the decisions made.

TABLE 1.1. Risk Factors for Venous Thromboembolic Disease in the Long Term Care Setting

Most Relevant Risk Factors

- Acute immobilization for more than 3 days
- CHF
- Latrogenic conditions
  - Central venous catheter or pacemaker
  - Chemotherapy
  - Erythropoiesis-stimulating agents
  - Estrogen
  - Heparin-induced thrombocytopenia
  - Hospital or LTC facility confinement
  - Major orthopedic surgery
  - Radiation therapy
- Lower-limb paresis
- Paralytic stroke (incidence of VTE ≈30–40%)

Other Risk Factors

- Acute MI (overall incidence of VTE ≈20%; elderly patients and those with infarction complicated by heart failure, recurrent angina, or ventricular arrhythmia are at greatest risk)
- Age over 40 years (risk increases exponentially with age)
- Hypercoagulable state
  - Activated protein C resistance/factor V Leiden mutation
  - Antiphospholipid antibodies
  - Antithrombin deficiency
  - Hyperhomocysteinemia
  - Protein C deficiency
  - Protein S deficiency
  - Prothrombin 20210 gene mutation
- Inflammatory bowel disease
- Malignancy (e.g., stomach, lung, pancreas)
- Nephrotic syndrome
- Obesity
- Previous DVT
- Recent surgery
- Severe COPD
- Severe or systemic infection
- Superficial vein thrombosis
- Trauma (e.g., pelvis, hip, leg fracture)
- Varicose veins

CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; LTC: long term care; MI: myocardial infarction; VTE: venous thromboembolism.

Adapted from Jacobs, 2003[16]; Geerts et al, 2008[22]; Heit et al, 2000[19]

TABLE 1.2. Steps in the Management of Antithrombotic Therapy in Elderly Patients

Step	Task(s)
1	Identify patients with conditions that may benefit from platelet-active medications (e.g., CAD, PAD, TIA, stroke).
2	Identify patients with conditions that may benefit from anticoagulant medications (e.g., AF, valvular heart disease, high risk for DVT or PE).
3	Record the diagnosis that justifies antiplatelet or anticoagulant therapy.
4	If warfarin is prescribed, establish and record target INR and INR range.*
5	If possible, estimate the patient's risk of a thrombotic event without antithrombotic treatment.*
6	If possible, estimate the reduction in the risk of a thrombotic event with effective antithrombotic treatment.*
7	Review the patient's history for absolute and relative contraindications to therapy.*†
8	Perform a baseline laboratory evaluation if one has not recently been completed (e.g., CBC, creatinine, glucose, INR, fecal occult blood test, urinalysis for blood). Consider optional stool test for *Helicobacter pylori* antigen.
9	Assess the patient for modifiable risk factors that increase the risk of bleeding during antithrombotic therapy (e.g., NSAIDs, *H. pylori*-associated ulcer, untreated urinary tract infection).
10	Reduce modifiable risk factors (e.g. stop NSAIDs, treat *H. pylori* infection, prescribe proton pump inhibitor to reduce the risk of gastrointestinal bleeding caused by antiplatelet medication).
11	Review the benefits and potential adverse effects of antithrombotic therapy with the patient and family or legally authorized representative and decide whether to begin therapy.
12	Monitor therapy for effectiveness (e.g., INR), if appropriate.
13	Monitor the patient for adverse effects of therapy (e.g., bleeding signs or symptoms; platelet count [for heparin or LMWH]; fecal occult blood test; hemoglobin [for anticoagulants and antiplatelet agents]).
14	Determine the appropriate duration of therapy and record a stop date.

AF: atrial fibrillation; CAD: coronary artery disease; CBC: complete blood count; DVT: deep vein thrombosis; INR: international normalized ratio; LMWH: low-molecular-weight heparin; NSAID: nonsteroidal anti-inflammatory drug; PAD: peripheral artery disease; PE: pulmonary embolism; TIA: transient ischemic attack.

* See Appendix 5, Baseline Anticoagulant Risk/Benefit Assessment
† See Appendix 12, Absolute Contraindications to Anticoagulation

The following principles may help to guide practitioners through the clinical decision-making process related to antithrombotic therapy.

1. Identify patients who are at risk for the development of thrombi and thromboemboli for whom thromboprophylaxis should be considered.

Patients who have a history of AF, coronary angioplasty, CAD, hemiparesis, hypercoagulable states, immobilization, MI, paralysis, peripheral arterial occlusive disease, recent surgery, recurrent DVT, stroke, TIA, or valvular heart disease all are candidates for thromboprophylaxis.

2. Assess the risks and benefits of antithrombotic therapy individually for each patient.

Patients at risk for thrombosis face the risk of adverse clinical events (e.g., DVT, MI, PE, stroke) if no antithrombotic therapy is prescribed. Antithrombotic therapy, however, is associated with a risk for adverse medication effects (e.g., serious bleeding and its consequences, including death). A decision aid such as the Baseline Antithrombotic Risk/ Benefit Assessment Tool (Appendix 5.4) can help the practitioner to quantify and document the potential benefits of antithrombotic therapy, relative and absolute contraindications to therapy, factors that increase the risk of bleeding, and baseline laboratory values.

3. Reduce the risk of complications caused by the use of antithrombotic medications.

To reduce the risk of adverse effects of antithrombotic medications, the practitioner should comply with published indications and contraindications, use recommended doses, monitor for adverse medication effects and, to the extent possible, modify risk factors associated with adverse medication effects. For example, bleeding risk may be reduced by treating peptic ulcer disease, if present, and by avoiding the use of nonsteroidal anti-inflammatory drugs.

4. Use the best available evidence and expert consensus to guide practice decisions.

Best practice in the use and monitoring of antithrombotic medications is constantly evolving. One measure of acceptable use for antithrombotic medications is approval by the FDA; however, in certain circumstances, practitioners may decide to use medications that are not specifically FDA-approved for a patient's individual circumstances. In these circumstances, prescribing decisions may be based on findings from high-quality clinical trials or evidence-based consensus guidelines issued by respected professional societies. Several such evidence-based guidelines from appropriate specialty societies, including *Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines* (published in February 2012) were consulted during the preparation of this Information Tool Kit. Information and recommendations in evidence-based guidelines and in this Information Tool Kit reflect the best advice available at the time of publication. The evidence base for antithrombotic therapy is continually growing and changing. Practitioners are encouraged to stay abreast of new developments and modify their practices accordingly.

5. Consider guideline recommendations in the context of the LTC patient's functional and cognitive status, prognosis, and previously stated goals for evaluation and treatment.

Ideally, decisions about evaluation and treatment should reflect the autonomous choices of a well-informed patient. If a patient lacks decision-making capacity, this limitation should be documented. If a legally authorized representative is designated for the patient, the rationale for the designation and any supporting legal documentation (e.g., advance directive, durable power of attorney for health care) should be included in the patient's medical record.

Documentation of decisions to forego assessment or treatment should summarize discussions with the patient, family, or legally authorized representative and relevant members of the multidisciplinary team. The medical record should reflect key elements of the decision-making process, including the diagnosis, prognosis, assessment, and treatment options (including refusal of assessment or treatment), as well as the possible benefits and burdens associated with those options.

Improving the Safety of Therapeutic Anticoagulation

Anticoagulant agents are among the most common medications implicated in adverse drug events (ADEs). In a study conducted at a major teaching hospital, most anticoagulant-associated ADEs resulted from medication errors; 30-day mortality was elevated among patients who suffered an anticoagulant-associated ADE.[23] Adverse events involving warfarin were implicated in 33.3% of emergency hospitalizations of U.S. adults aged 65 or older.[24] Adverse events involving oral antiplatelet agents accounted for a further 13.3% of such hospitalizations. Nearly half of all of the emergency hospitalizations for adverse drug events identified in the study oc-

curred among adults aged 80 or older. Recommendations for improving the safety of therapeutic anticoagulation developed for the acute-care setting may also assist LTC facilities in reducing adverse events involving these commonly prescribed medications (Table 1.3). (Please refer also to AMDA's *Multidisciplinary Medication Management Manual* for guidance on safe medication use in the LTC setting.[a])

TABLE 1.3. Improving the Safety of Therapeutic Anticoagulation: Joint Commission National Patient Safety Goals 2012

- Use only oral unit-dose products and prefilled syringes when these types of products are available.
- Use approved protocols for the initiation and maintenance of anticoagulant therapy.
- Assess the patient's anticoagulation status before initiating warfarin therapy.
- For all patients receiving warfarin, adjust therapy on the basis of a current INR value.
- Use authoritative resources to manage potential food and drug interactions in patients receiving warfarin.
- Develop and implement a written policy to address baseline and ongoing laboratory tests required to monitor patients on anticoagulant therapy.
- Educate prescribers, staff, patients, and families about anticoagulant therapy. Patient and family education should include the following:
  - Importance of follow-up monitoring
  - Importance of adherence to therapy
  - Drug-food interactions
  - Potential for adverse drug reactions and interactions
- Evaluate anticoagulation safety practices, take action to improve these practices, and measure the effectiveness of those actions in a time frame determined by the facility.

INR, international normalized ratio.

Adapted from: The Joint Commission[25]

Using the American College of Chest Physicians Recommendations

Whenever possible, recommendations in this Information Tool Kit are graded according to the schema used by the American College of Chest Physicians (ACCP) in its evidence-based guidelines for antithrombotic therapy and prevention of thrombosis (Table 1.4).[26] The ACCP grades recommendations for antithrombotic agents and therapeutic interventions using explicit evidence-based criteria. Recommendations are either strong (Grade 1) or weak (Grade 2). Within these two categories, recommendations are graded A, B, or C according to the quality of available evidence from randomized controlled trials or observational studies.

For practitioners and patients faced with the task of deciding whether to accept ACCP recommendations and add them to a treatment plan, the following guidance may be helpful:

- A **strong** recommendation (Grade 1) means that the intervention or treatment is appropriate for most patients. Thus, absent important mitigating factors, most patients should receive this intervention. If the practitioner or patient decides to forego an intervention backed by a strong recommendation, he or she should document the rationale for this decision.

[a] AMDA. *Multidisciplinary Medication Management Manual.* Ordering information available at http://www.amda.com/resources/index.cfm.

- A **weak** recommendation (Grade 2) is one that most people would probably choose, but many would not. Practitioners are encouraged to discuss the pros and cons of a weak recommendation and document the decision process. This discussion may benefit from the use of decision aids, if available and appropriate.

TABLE 1.4. American College of Chest Physicians Approach to Grades of Recommendations

Grade of Recommendation	Risk/Benefit Considerations	Methodological Strength of Supporting Evidence	Clinical Implications
1A Strong recommendation, high-quality evidence	Desirable effects clearly outweigh undesirable effects or vice versa	RCTs with consistent results and without important limitations ***or*** exceptionally strong evidence from observational studies	• Recommendation can apply to most patients in most circumstances • Further research very unlikely to alter confidence in estimate of effect
1B Strong recommendation, moderate-quality evidence	Desirable effects clearly outweigh undesirable effects or vice versa	RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise) ***or*** very strong evidence from observational studies	• Recommendation can apply to most patients in most circumstances • Higher-quality research may alter estimate of effect
1C Strong recommendation, low- or very low-quality evidence	Desirable effects clearly outweigh undesirable effects or vice versa	Observational studies, case series, or RCTs with important limitations	• Recommendation can apply to most patients in many circumstances • Higher-quality research may well alter estimate of effect
2A Weak recommendation, high-quality evidence	Desirable effects closely balanced with undesirable effects	RCTs with consistent results and without important limitations ***or*** exceptionally strong evidence from observational studies	• Best action may depend on circumstances or patient or societal values • Further research very unlikely to alter confidence in estimate of effect
2B Weak recommendation, moderate-quality evidence	Desirable effects closely balanced with undesirable effects	RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise) ***or*** very strong evidence from observational studies	• Best action may depend on circumstances or patient or societal values • Higher-quality research may alter estimate of effect
2C Weak recommendation, low- or very low-quality evidence	• Uncertainty in estimates of benefits, risks, and burdens • Desirable and undesirable effects may be closely balanced	Observational studies, case series, or RCTs with important limitations	• Other alternatives may be equally reasonable • Higher-quality research may well alter estimate of effect

RCTs: randomized clinical trials.

Adapted from Guyatt et al, 2012[26]

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2. PREVENTION OF VENOUS THROMBOEMBOLISM

Many patients in the long term care (LTC) setting, especially those who have recently been hospitalized, have risk factors for venous thromboembolism (VTE). It is difficult to predict precisely which at-risk patients will develop VTE, and screening at-risk patients for the development of VTE is not cost-effective. Timely diagnosis of VTE is further confounded by the fact that both deep vein thrombosis (DVT) and pulmonary embolism (PE) may be initially asymptomatic or may present with vague, nonspecific symptoms. Because of the high cost and impracticality of VTE screening, routine prophylaxis for those at moderate and high risk is preferable to a "diagnose-and-treat" approach. Many studies confirm that prophylactic anticoagulation is safe and prevents DVT, PE, and death from PE.

Practitioners who manage oral anticoagulation therapy in the LTC facility should do so in a systematic and coordinated way that encompasses patient and staff education, systematic international normalized ratio (INR) testing, tracking with the use of the tools presented in this manual, and appropriate timely follow-up.[1] A modest amount of staff education has been found to significantly improve adherence to practice guidelines for risk assessment and initiation of therapy to prevent DVT and thromboembolism. For example, in one study, investigators assessed current antithrombotic practices in 376 newly admitted or readmitted patients aged a mean of 77 years at 17 LTC facilities. Facility medical directors were provided with clinical guidance on VTE prevention in the LTC setting developed by the study team, along with other education and information tools. Of the 376 admission, 85% had medical or postsurgical indications that would normally warrant prophylactic anticoagulant therapy, although there were a significant number of contraindications, such as abbreviated life expectancy or history of bleeding, that presented contraindication for therapy. Two-thirds of the patients with indications for prophylaxis received therapy, including many with contraindications. Following staff education, standards consistent with current clinical practice guidelines were met in 82% of cases. Other indicators of improvement in care, such as a reduction in the prescribing of additional medications to patients who were already taking anticoagulants for atrial fibrillation, also emerged. In addition, non-drug prophylactic measures consistent with current guidelines were more likely to be followed after the educational intervention.[2]

Table 2.1 summarizes the absolute risk for DVT in the absence of thromboprophylaxis in various clinical situations. Appendixes 1, 2, and 3 provide tools to assist the practitioner in assessing thrombosis risk, selecting a thromboprophylaxis regimen based on risk factors, and assessing the safety of thromboprophylaxis.

Weighing Benefits and Burdens: Number Needed to Treat and Number Needed to Harm

One clinically meaningful way to understand the benefits and risks of VTE prophylaxis is to consider the number needed to treat (NNT) or number needed to harm (NNH). These calculations show how many patients must receive thromboprophylaxis for one patient to experience a given benefit (NNT) or negative outcome (NNH). For example, for every seven surgical patients receiving thromboprophylaxis, one DVT will be prevented—an NNT of 7.[3] Similarly, for surgical patients, the NNT to prevent one symptomatic PE is 143; to prevent one fatal PE, 182.[3] While major bleeding rates are statistically the same for thromboprophylaxis groups and controls, the NNH for wound hematoma is 45; that is, for every 45 patients treated with thrombo-

TABLE 2.1. Absolute Risk of Deep Venous Thrombosis in the Absence of Thromboprophylaxis*

Condition	Estimated Prevalence of Deep Vein Thrombosis (%)
Spinal cord injury	60–80
Major trauma	40–80
Critical care patients	10–80
Orthopedic surgery (hip or knee arthroplasty, hip fracture)	40-60
Stroke	20–50
General surgery Major gynecological surgery Major urologic surgery Neurosurgery	15–40
Medical patients	10–20

*Rates are based on objective diagnostic testing for deep vein thrombosis in patients, not on thromboprophylaxis.

Adapted from Geerts et al, 2008[3]

prophylaxis, one additional wound hematoma is likely to occur.[3] Combining these statistics to place benefits and burdens into perspective, studies show that for every 180 postoperative patients who receive thromboprophylaxis, approximately 25 DVTs and one fatal PE will be prevented, whereas patients will experience four additional wound hematomas.

Thromboprophylaxis for Postsurgical Patients

States of reduced blood flow that occur during surgery, surgical damage to the vasculature, and postoperative immobilization can contribute to thrombus formation. The risk of developing postoperative DVT is highest within the first week or two after surgery. VTE complications, including fatal PE, may occur up to 30 days later, particularly in patients with hip fracture.

Risk of VTE, and thus need for surgical thromboprophylaxis, varies according to risk category (see Table 2.1). Patients who remain fully mobile and undergo minor surgical procedures are at low risk (less than 10%) for VTE.[3] Open gynecologic or urologic surgery and general surgery present moderate (15% to 40%) VTE risk.[3] Major trauma, surgery for hip fracture, and arthroplasty of the hip or knee create a high risk (40% to 80%) for VTE.[3] The highest-risk surgical patients are those undergoing cancer surgery and those general surgery patients with a history of VTE. Table 2.2 summarizes the current American College of Chest Physicians (ACCP) recommendations for thromboprophylaxis in nonorthopedic surgical patients on the basis of risk.

The availability of anticoagulants with oral dosage forms could simplify medication regimens for patients receiving VTE prophylaxis after hospital discharge. Currently, warfarin and rivaroxaban are the only two FDA-approved oral agents for postoperative VTE prophylaxis.[4] Warfarin is less effective than low-molecular-weight heparin (LMWH) for preventing VTE; it also requires frequent and complex monitoring. By contrast, rivaroxaban is more effective than LMWH for VTE prophylaxis. According to phase III trials, rivaroxaban does not increase the risk of major bleeding compared with other agents, and it has been studied in extended-duration prophylaxis. Dabigatran has efficacy equivalent to that of LMWH in patients undergoing hip replacement, but not in those undergoing knee replacement surgery.

Thromboprophylaxis for Medical Patients

Medical patients with reduced mobility have substantial risks for VTE. Optimizing ambulation (unless contraindicated or not feasible) should be part of the treatment plan. The current ACCP recommendations on thromboprophylaxis in nonsurgical patients are summarized in Table 2.2. ACCP 2012 recommends prophylaxis with LMWH, low-dose unfractionated heparin bid or tid, or fondaparinux (Grade 1B) and suggests against the use of thromboprophylaxis beyond the time of the patient's immobilization or acute hospital stay (Grade 2B). Neither pharmacologic nor mechanical prophylaxis is recommended for acutely ill hospitalized medical patients at low risk of thrombosis (Grade 1B). For those at increased risk of thrombosis who are bleeding or at risk for major bleeding, the use of graduated compression stockings or intermittent pneumatic compression is suggested (Grade 2C). For critically ill patients, the use of LMWH or low-dose unfractionated heparin is suggested (Grade 2C). The use of graduated compression stockings or intermittent pneumatic compression is recommended for critically ill patients who are bleeding or are at high risk for major bleeding (Grade 2C).[5]

Risk of VTE persists after discharge to subacute care[6] and LTC facilities.[7,8] However, because no studies exist to clarify the benefits and risks of prolonged prophylaxis for these patients, the ACCP does not make a recommendation about extended prophylaxis for LTC patients after hospital discharge, nor does the ACCP address thromboprophylaxis for patients with acute medical illnesses who are treated within the LTC facility.

Ten trials evaluated a total of 20,717 medical patients without stroke to compare the use of heparin prophylaxis with no heparin prophylaxis. The results showed that heparin prophylaxis was not associated with a statistically significant reduced risk for mortality but was associated with a reduced risk for PE; bleeding risk, however, increased. Heparin prophylaxis was also associated with an absolute reduction of two fewer symptomatic DVTs per 1000 patients treated—a numerical, though not statistically significant, finding.[9]

The PROTECT trial, a randomized multicenter trial that enrolled 3,764 patients in intensive care units, was designed to compare the effects of thromboprophylaxis with LMWH and unfractionated heparin (UFH) on VTE, bleeding, and other outcomes in critically ill patients. No significant difference was found in the rate of proximal leg DVT between patients treated with UFH (5.8%) and those treated with dalteparin (5.1%). The proportion of patients with PE was significantly lower in the group treated with dalteparin (1.3% vs. 2.3% in the group treated with UFH). No major difference was seen in major bleeding rates or deaths in the hospital. Finally, patients receiving dalteparin had a lower rate of heparin-induced thrombocytopenia. The investigators concluded that among critically ill patients, dalteparin was not superior to UFH in decreasing the incidence of proximal DVT.[10]

TABLE 2.2. ACCP Recommendations on Thromboprophylaxis in Nonorthopedic Surgical Patients and Nonsurgical Patients

Note: * denotes agents with an FDA-approved indication for VTE prophylaxis. Among the LMWHs, enoxaparin and dalteparin are FDA approved for this indication.

Patient Category	Strong Recommendations	Weak Recommendations
General and abdominal-pelvic surgery patients		
Very low risk for VTE (less than 0.5%; Rogers score, less than 7; Caprini score, 0)		No specific pharmacologic (Grade 1B) or mechanical (Grade 2C) prophylaxis other than early ambulation
Low risk for VTE (~1.5%; Rogers score, 7–10; Caprini score, 1–2)		Mechanical prophylaxis, preferably with IPC, over no prophylaxis (Grade 2C)
Moderate risk for VTE (~3.0%; Rogers score, more than 10; Caprini score, 3–4), not at high risk for major bleeding complications		• LMWH (enoxaparin*, dalteparin*) (Grade 2B), • LDUH* (Grade 2B), or • Mechanical prophylaxis, preferably with IPC (Grade 2C), over no prophylaxis
Moderate risk for VTE (3.0%; Rogers score, more than 10; Caprini score, 3–4), at high risk for major bleeding complications, ***or*** for whom consequences of bleeding may be particularly severe		• Mechanical prophylaxis, preferably with IPC, over no prophylaxis (Grade 2C) • Mechanical prophylaxis with ES or IPC should be added to pharmacologic prophylaxis (Grade 2C)
High risk for VTE, undergoing abdominal or pelvic surgery for cancer, not otherwise at high risk for major bleeding complications	Extended-duration pharmacologic prophylaxis (4 wk) with LMWH (enoxaparin*, dalteparin*) over limited-duration prophylaxis (Grade 1B)	
High risk for VTE, at high risk for major bleeding complications, ***or*** for whom consequences of bleeding may be particularly severe		Mechanical prophylaxis, preferably with IPC, over no prophylaxis until risk of bleeding diminishes and pharmacologic prophylaxis may be initiated (Grade 2C)
High risk for VTE (6%; Caprini score, 5 or above), both LMWH and UFH contraindicated or unavailable, ***and*** not at high risk for major bleeding complications		• Low-dose aspirin (Grade 2C), fondaparinux (Grade 2C), or • Mechanical prophylaxis, preferably with IPC (Grade 2C) over no prophylaxis
General and abdominal-pelvic surgery		• IVC filter should not be used for primary VTE prevention (Grade 2C) • Periodic surveillance with VCU should not be performed (Grade 2C)
Cardiac surgery patients		
Uncomplicated postoperative course		Mechanical prophylaxis, preferably with optimally applied IPC, over either no prophylaxis (Grade 2C) or pharmacologic prophylaxis (Grade 2C)
Hospital course prolonged by one or more nonhemorrhagic surgical complications		Pharmacologic prophylaxis with LDUH* or LMWH (enoxaparin*, dalteparin*) in addition to mechanical prophylaxis (Grade 2C)

TABLE 2.2 Continued
Recommendations on Thromboprophylaxis in Nonorthopedic Surgical Patients and Nonsurgical Patients
Note: * denotes agents with an FDA-approved indication for VTE prophylaxis. Among the LMWHs, enoxaparin and dalteparin are FDA approved for this indication.

Patient Category	Strong Recommendations	Weak Recommendations
Thoracic surgery patients		
Moderate risk for VTE, not at high risk for perioperative bleeding		• LDUH* (Grade 2B), • LMWH (enoxaparin*, dalteparin*) (Grade 2B), or • Mechanical prophylaxis with optimally applied IPC (Grade 2C) over no prophylaxis
High risk for VTE, not at high risk for perioperative bleeding	LDUH* (Grade 1B) or LMWH (enoxaparin*, dalteparin*) (Grade 1B) over no prophylaxis	Add mechanical prophylaxis with ES or IPC to pharmacologic prophylaxis (Grade 2C)
High risk for major bleeding		Mechanical prophylaxis, preferably with optimally applied IPC, over no prophylaxis until risk of bleeding diminishes and pharmacologic prophylaxis may be initiated (Grade 2C)
Craniotomy		
All		Mechanical prophylaxis, preferably with IPC, over no prophylaxis (Grade 2C) or pharmacologic prophylaxis (Grade 2C)
Very high risk for VTE (e.g., undergoing craniotomy for malignant disease)		Add pharmacologic prophylaxis to mechanical prophylaxis once adequate hemostasis is established and risk of bleeding decreases (Grade 2C)
Major trauma		
All		• LDUH (Grade 2C), LMWH (Grade 2C), or mechanical prophylaxis, preferably with IPC (Grade 2C), over no prophylaxis • IVC filter should not be used for primary VTE prevention (Grade 2C) • Periodic surveillance with VCU should not be performed (Grade 2C)
High risk for VTE (e.g., acute spinal cord injury, traumatic brain injury, spinal surgery for trauma)		Add mechanical prophylaxis to pharmacologic prophylaxis (Grade 2C) when not contraindicated by lower-extremity injury
LMWH, LDUH contraindicated		• Mechanical prophylaxis, preferably with IPC, over no prophylaxis (Grade 2C) when not contraindicated by lower-extremity injury • Add pharmacologic prophylaxis with either LMWH or LDUH when risk of bleeding diminishes or contraindication to heparin resolves (Grade 2C)

TABLE 2.2 Continued
Recommendations on Thromboprophylaxis in Nonorthopedic Surgical Patients and Nonsurgical Patients

Note: * denotes agents with an FDA-approved indication for VTE prophylaxis. Among the LMWHs, enoxaparin and dalteparin are FDA approved for this indication.

Patient Category	Strong Recommendations	Weak Recommendations
Prevention of VTE in Nonsurgical Patients		
Acutely ill, hospitalized medical patients		
Increased risk of thrombosis	Anticoagulant thromboprophylaxis with LMWH (enoxaparin*, dalteparin*), LDUH* bid, LDUH* tid, or fondaparinux (Grade 1B)	
Low risk of thrombosis	Do not use pharmacologic or mechanical prophylaxis (Grade 1B)	
Bleeding or at high risk for bleeding	Do not use anticoagulant thromboprophylaxis (Grade 1B)	
Increased risk of thrombosis ***and*** bleeding or at high risk for major bleeding		• Optimal use of mechanical thromboprophylaxis with GCS (Grade 2C) ***or*** IPC (Grade 2C) rather than no mechanical thromboprophylaxis • When bleeding risk decreases ***and*** if VTE risk persists, substitute pharmacologic thromboprophylaxis for mechanical thromboprophylaxis (Grade 2B)
Treated with initial course of thromboprophylaxis		Do not extend duration of thromboprophylaxis beyond period of patient immobilization or acute hospital stay (Grade 2B)
Critically ill patients		
All		• Do not routinely use ultrasound screening for DVT (Grade 2C) • LMWH (enoxaparin*, dalteparin*) or LDUH* thromboprophylaxis over no prophylaxis (Grade 2C)
Bleeding or at high risk for major bleeding		• Mechanical thromboprophylaxis with GCS (Grade 2C) or IPC (Grade 2C) until bleeding risk decreases, rather than no mechanical thromboprophylaxis • When bleeding risk decreases, pharmacologic thromboprophylaxis may be substituted for mechanical thromboprophylaxis (Grade 2C)

TABLE 2.2 Continued
Recommendations on Thromboprophylaxis in Nonorthopedic Surgical Patients and Nonsurgical Patients

Note: * denotes agents with an FDA-approved indication for VTE prophylaxis. Among the LMWHs, enoxaparin and dalteparin are FDA approved for this indication.

Patient Category	Strong Recommendations	Weak Recommendations
Patients with cancer		
No additional risk factors for VTE	No prophylactic use of VKAs (Grade 1B)	No routine prophylaxis with LMWH or LDUH (Grade 2B)
Solid tumors, additional risk factors for VTE (e.g., previous VTE, immobilization, hormonal therapy, angiogenesis inhibitors, thalidomide, lenalidomide), low risk of bleeding		Prophylactic-dose LMWH (enoxaparin*, dalteparin*) or LDUH* over no prophylaxis (Grade 2B)
Indwelling central venous catheters		• No routine prophylaxis with LMWH or LDUH (Grade 2B) • No prophylactic use of VKAs (Grade 2C)
Other		
Chronically immobilized persons residing at home or at a nursing home		***Against*** routine use of thromboprophylaxis (Grade 2C)
Long-distance travelers at increased risk of VTE (including previous VTE, recent surgery or trauma, active malignancy, pregnancy, estrogen use, advanced age, limited mobility, severe obesity, or known thrombophilic disorder)		• Frequent ambulation, calf muscle exercise, or sitting in an aisle seat if feasible (Grade 2C) • Use of properly fitted, below-knee GCS providing 15 to 30 mm Hg of pressure at the ankle during travel (Grade 2C) • For all other long-distance travelers, suggest against the use of GCS (Grade 2C)
Asymptomatic thrombophilia (i.e., no previous history of VTE)	No long-term daily use of mechanical or pharmacologic thromboprophylaxis to prevent VTE (Grade 1C)	

ES: elastic stockings; GCS: graduated compression stockings; IPC: intermittent pneumatic compression; IVC: inferior vena cava; LDUH: low-dose unfractionated heparin; LMWH: low-molecular-weight heparin; UFH: unfractionated heparin; VCU: venous compression ultrasonography; VKA: vitamin K antagonist; VTE: venous thromboembolism.

Adapted from: Gould et al, 2012[11]; Kahn et al, 2012[5]

Thromboprophylaxis for Orthopedic Surgery Patients

It is well established that orthopedic surgery increases VTE incidence. The challenge has been to optimize prophylaxis while accounting for type of surgery, available agents, and duration of prophylaxis. This task is further compounded when the patient's comorbidities, personal preferences, and even costs of therapies are considered.

Different expert groups examining the evidence have reached differing conclusions. For example, the Cochrane Collaboration concluded that patients with lower-leg immobilization should receive VTE prophylaxis,[12] whereas the ACCP did not.[13] Where such differences of opinion exist, the prescribing practitioner should consider the recommendations of expert groups while also taking into account the patient's coexisting clinical conditions and preferences, and should select the course of action most appropriate for that patient. In the LTC setting, regardless of which expert guideline the practitioner uses, bleeding risks and benefits of VTE prophylaxis must be assessed for each patient.

The ACCP panel found that at 35 days postoperatively, the cumulative, nonfatal rate of symptomatic VTE in orthopedic patients receiving no prophylaxis was 4.3%, compared with 1.8% in patients receiving prophylaxis with LMWH.[13] Studies suggest that LMWH may reduce the incidence of symptomatic VTE to 13 per 1,000 patients treated, compared with 16 per 1,000 with low-dose unfractionated heparin (LDUH), without an increase in major bleeding. For other agents, the risk of bleeding varies.[13] This was recently confirmed by a systematic review finding that prolonged treatment decreases VTE risk. Although the risk of bleeding also increases, the overall benefits of prevention outweigh the risk.[14]

The American Academy of Orthopaedic Surgeons (AAOS) reviewed the risk of bleeding for patients undergoing elective total hip arthroplasty (THA) or total knee arthroplasty (TKA) and found inconclusive evidence that factors other than a known bleeding disorder or active liver disease increase the risk of bleeding. Thus, AAOS was unable to recommend for or against the use of other factors to determine an individual patient's risk of bleeding.[15]

For all major orthopedic surgery, ACCP recommends thromboprophylaxis for a minimum of 10 to 14 days (Grade 1B for pharmacologic prophylaxis, 1C for intermittent pneumatic compression) and suggests extending prophylaxis for up to 35 days from the day of surgery (Grade 2B).[13]

For patients with lower-leg injuries distal to the knee requiring leg immobilization, including fractures below the knee, tendon ruptures, and cartilage injuries of the knee and ankle, ACCP recommends no prophylaxis.[13] By contrast, a Cochrane systematic review concluded that LMWH can safely be used to prevent VTE in adult patients with immobilization of the lower leg, including both those with above- and below-knee casts, and recommended that this use be considered. The Cochrane reviewers further recommended continuation of treatment with LMWH for the entire period of immobilization of the lower extremity.[12]

The ACCP panel reviewed this Cochrane analysis as well as an additional multicenter study and performed its own analysis to reach its conclusion that prophylaxis is not needed in the setting of lower-leg immobilization. The ACCP panel noted, however, that high-risk populations were excluded from the studies it reviewed. Although patients residing in the LTC setting may be a higher-risk group, they also in most cases have multiple comorbidities; for this reason, bleeding risk may outweigh the benefit of prophylaxis in the setting of lower-limb immobilization.

Practitioners should be aware that, although LMWH has been the preferred agent for thromboprophylaxis in the setting of major orthopedic surgery in the absence of contraindications, rivaroxaban, a direct inhibitor of factor Xa, has also been studied for thromboprophylaxis after total hip or knee arthroplasty. The results of a recent systematic review suggest that factor Xa inhibitors may be more effective, especially if used at low doses to decrease bleeding risk.[16] Although the review authors did not quantify "low dose," many of the rivaroxaban studies included in the review used 10 mg daily.[16] In the RECORD (Regulation of Coagulation in Major Orthopedic surgery Reducing the Risk of DVT and PE) program of four clinical trials (two involving total hip replacement surgery and two involving total knee replacement surgery), rivaroxaban was compared with enoxaparin for VTE prevention. Approximately 15% of the 9,011 patients enrolled in the RECORD 1, 2, and 3 trials were aged over 75. A pooled analysis of trials 1, 2, and 3 showed that during the 2-week active, controlled period, rivaroxaban significantly reduced symptomatic VTE and all-cause mortality by 56% (0.4% vs. 0.8%). The two agents had similar safety profiles.[17-19] Factor Xa inhibitors should be avoided, however, in patients with creatinine clearance (CrCl) below 30 ml/min. Renal function must be evaluated when the use of factor Xa inhibitors is being considered in the LTC setting.

Tables 2.3 and 2.4 summarize, respectively, current recommendations from the ACCP and AAOS for antithrombotic prophylaxis to prevent VTE in patients undergoing major orthopedic surgery, and recommendations from the North American Spine Society to prevent VTE in patients undergoing elective spine surgery.

TABLE 2.3. American College of Chest Physicians and American Association of Orthopedic Surgeons Recommendations for Antithrombotic Prophylaxis to Prevent Venous Thromboembolism in Patients Undergoing Major Orthopedic Surgery

Note: * denotes agents with an FDA-approved indication for orthopedic prophylaxis. Enoxaparin is FDA approved for TKA and THA; dalteparin for THA; fondaparinux for THA or hip repair, TKA; rivaroxaban for TKA and hip repair. Warfarin is FDA approved for VTE prophylaxis but not specifically for orthopedic procedures.

Patient Category	ACCP Recommendations	AAOS Recommendations§
Total hip or knee arthroplasty	• Use one of the following for at least 10–14 days: ○ LMWH*, fondaparinux*, apixaban, dabigatran, rivaroxaban, LDUH*, adjusted-dose VKA, aspirin (all Grade 1B), or ○ IPCD (Grade 1C) • Start LMWH 12 h or more preoperatively or 12 h or more postoperatively (Grade 1B) • Irrespective of concomitant use of IPCD, LMWH is preferred over other agents (fondaparinux, apixaban, dabigatran, rivaroxaban, LDUH: all Grade 2B; adjusted-dose VKA, aspirin: Grade 2C) • Extend thromboprophylaxis in outpatient period for up to 35 days from day of surgery (Grade 2B) • Use dual prophylaxis with antithrombotic agent and IPCD during hospital stay (Grade 2C) *Note: As of July 2012, apixaban is not FDA approved for any indication in the United States.*	• ***Against*** routine postoperative duplex ultrasonography screening (Grade: Strong) • Practitioner might further assess VTE risk by determining whether patient had previous VTE (Grade: Weak) • Assess for known bleeding disorders and presence of active liver disease (Grade: Consensus) • Discontinue antiplatelet agents (e.g., aspirin, clopidogrel) before surgery (Grade: Moderate) • Patients not at elevated risk for VTE: Use pharmacologic prophylaxis and/or mechanical compressive devices (Grade: Moderate) • Patient and practitioner should discuss duration of prophylaxis (Grade: Consensus) • Patients with history of VTE: Use pharmacologic prophylaxis and mechanical compressive devices (Grade: Consensus) • Patients with known bleeding disorder: Use mechanical compressive devices (Grade: Consensus) • Early mobilization (Grade: Consensus) • Neuraxial anesthesia (intrathecal, epidural, spinal) (Grade: Moderate)
Hip fracture surgery	• Use one of the following for at least 10–14 days: ○ LMWH, fondaparinux*, LDUH, adjusted-dose VKA, aspirin (all Grade 1B), or ○ IPCD (Grade 1C) • Irrespective of concomitant IPCD use or duration of treatment, LMWH is preferred over other agents (fondaparinux, LDUH: Grade 2B; adjusted-dose VKA, aspirin: Grade 2C) • Extend thromboprophylaxis for up to 35 days from day of surgery (Grade 2B) • Use dual prophylaxis with antithrombotic agent and IPCD during hospital stay (Grade 2C) • Administer LMWH at least 12 h before surgery (not graded)	

TABLE 2.3 Continued
American College of Chest Physicians and American Association of Orthopedic Surgeons Recommendations for Antithrombotic Prophylaxis to Prevent Venous Thromboembolism in Patients Undergoing Major Orthopedic Surgery

Note: * denotes agents with an FDA-approved indication for orthopedic prophylaxis. Enoxaparin is FDA approved for TKA and THA; dalteparin for THA; fondaparinux for THA or hip repair, TKA; rivaroxaban for TKA and hip repair. Warfarin is FDA approved for VTE prophylaxis but not specifically for orthopedic procedures.

Patient Category	ACCP Recommendations	AAOS Recommendations[§]
Major orthopedic surgery (THA, TKA, or HFS) ***and*** increased risk of bleeding	• Use IPCD or no prophylaxis (Grade 2C) • Endeavor to achieve 18 h per day of compliance with IPCD use • Do not use IVC filter placement for primary prevention over no thromboprophylaxis in patients with increased bleeding risk or contraindications to pharmacologic and mechanical thromboprophylaxis (Grade 2C)	
Major orthopedic surgery (THA, TKA, or HFS) ***and*** patient declines or is uncooperative with injections or IPCD	Use apixaban or dabigatran (substitute rivaroxaban or adjusted-dose VKA if apixaban or dabigatran unavailable)[†] (Grade 1B) *Note: As of July 2012, apixaban is not FDA approved for any indication in the United States.*	
Asymptomatic patients following major orthopedic surgery	Do not use Doppler or duplex ultrasound screening before hospital discharge (Grade 1B)	
Patients with isolated lower-leg injuries requiring leg immobilization	No thromboprophylaxis (Grade 2C)	
Patients undergoing knee arthroscopy with no history of VTE	No thromboprophylaxis (Grade 2B)	

HFS: hip fracture surgery; IPCD: intermittent pneumatic compression device; IVC: inferior vena cava; LDUH: low-dose unfractionated heparin; LWMH: low-molecular-weight heparin; THA: total hip arthroplasty; TKA: total knee arthroplasty; TKR: total knee replacement; VKA: vitamin K antagonist; VTE: venous thromboembolism.

[§] AAOS guideline[15] addresses VTE prophylaxis in THA and TKA only. Recommendations are graded as "Strong" (at least two high-quality studies); "Moderate" (at least two moderate-quality studies); "Weak" (at least two low-quality studies); or "Consensus" (very low-quality studies).

[†] Evaluate renal function. Avoid these agents in patients with CrCl below 30 ml/min.

Adapted from: Falck-Ytter et al, 2012[13]; AAOS, 2011[15]

TABLE 2.4. American College of Chest Physicians and North American Spine Society* Recommendations for Antithrombotic Prophylaxis to Prevent Venous Thromboembolism in Patients Undergoing Elective Spine Surgery

Note: No agents have been FDA approved for an indication of spinal surgery.

Patient Category	ACCP Recommendations	AAOS Recommendations†
Spinal surgery	• Mechanical prophylaxis, preferably with IPC, over no prophylaxis (Grade 2C), unfractionated heparin (Grade 2C), or LMWH (Grade 2C) • **Comment:** Expected reduction in VTE events is similar with all methods. For low-risk patients, VTE reductions are countered by a similar increase in bleeding complications with anticoagulants and skin complications with mechanical methods. Balance in favor of prophylaxis is greatest for patients at moderate and high risk of VTE.	
High risk of VTE	• Add pharmacologic prophylaxis to mechanical prophylaxis once adequate hemostasis is established and risk of bleeding decreases (Grade 2C) • **Comment:** Other risk factors for VTE with spine surgery include older age, prior VTE, multiple operative levels	• LMWH (Grade: Consensus) • Low-dose† warfarin **Comments:** • "High risk" defined as multiple trauma, malignancy, or hypercoagulable state (Grade: Consensus) • Treatment can start day of surgery; no duration given (Grade: Consensus)
Combined anterior-posterior approach procedures	Add pharmacologic prophylaxis to mechanical prophylaxis once adequate hemostasis is established and risk of bleeding decreases (Grade 2C)	• LMWH (Grade: Consensus) • Low-dose† warfarin **Comments:** • Consider chemoprophylaxis with LMWH in patients with high risk for VTE (e.g., those with multiple trauma, malignancy, hypercoagulable state) (Grade: Consensus) • Treatment can start day of surgery; no duration specified (Grade: Consensus)
Posterior-approach procedures		• Chemoprophylaxis not recommended (Grade: Consensus) • Mechanical compression devices in lower extremities (Grade: B) **Comments:** • Bleeding risk outweighs benefits (Grade: Consensus) • Start treatment just prior to surgery and continue until patient is ambulatory (Grade: Consensus)

IPC: intermittent pneumatic compression; LMWH: low-molecular-weight heparin; VTE: venous thromboembolism.

* North American Spine Society recommendations were graded according to the following scheme:
A. Good evidence (Level I studies with consistent findings) for or against recommending intervention
B. Fair evidence (Level II or III studies with consistent findings) for or against recommending intervention
C. Poor-quality evidence (Level IV or V studies) for or against recommending intervention
I. Insufficient or conflicting evidence not allowing a recommendation for or against intervention
Consensus: Level I-IV evidence insufficient to support a recommendation; recommendation based only on expert consensus

† "Low-dose" not defined

Adapted from: Gould et al, 2012[11]; North American Spine Society, 2009[20]; Bono et al, 2009[21]

Thromboprophylaxis After a Stroke

The PREVAIL trial provided evidence that routine use of a prophylactic dose of LMWH in immobile patients was useful for VTE prevention after stroke.[22] The trial's primary endpoint was VTE incidence at day 14 in patients with ischemic stroke with leg weakness of at least 2 on the National Institutes of Health Stroke Scale (NIHSS). These patients were randomized in an open-label fashion to receive 5,000 units of UFH twice daily or 40 mg of enoxaparin daily, starting within 48 hours of the event and continuing for 10 days. Compared with UFH, enoxaparin was associated with a significant 43% relative risk reduction in VTE events. This translates to eight fewer strokes per 100 patients treated and an NNT of 13. Regardless of treatment, patients who had had a more severe stroke (defined as one with an NIHSS score of 14 or higher) were twice as likely to have VTE and were at higher risk of having bleeding complications.

Evidence from eight trials with a total of 15,405 patients with acute stroke that compared heparin prophylaxis with no heparin prophylaxis showed that heparin prophylaxis was not associated with a statistically significant reduction in risk for mortality, PE, or symptomatic DVT. Heparin prophylaxis was associated with an increased risk for major bleeding events. The pooled trials were heterogeneous in their patient samples and treatment. The strongest evidence on the benefits and harms of VTE prophylaxis came from a single large, randomized, controlled trial of patients with acute ischemic stroke with 14,578 enrolled patients. It found no statistically significant difference between low-dose heparin and no heparin in 14-day all-cause mortality, fatal PE, or all (fatal and non-fatal) PEs. The study showed a statistically significant increase in 14-day hemorrhagic stroke or serious extracranial hemorrhage and a statistically significant decrease in 14-day recurrent ischemic stroke.[9]

The applicable recommendations of the ACCP are as follows: for the prevention of stroke recurrence after an acute stroke, aspirin therapy at a dose of 160 mg to 325 mg should be given within 48 hours after an acute stroke (Grade 1A). After 1 to 2 weeks of acute therapy, the starting dose of aspirin should be reduced to the maximum secondary-prevention dose of 75 mg to 100 mg daily.

For VTE prevention in patients with restricted mobility, the ACCP recommends prophylactic-dose heparin therapy begun within 48 hours after stroke and continued until the end of the hospital stay or the patient regains mobility (Grade 2B). LMWH is preferred over UFH (Grade 2B). The ACCP makes no recommendations regarding the continuation of these interventions through the transition to a subacute or LTC setting. Combining pharmacologic therapy with intermittent pneumatic compression devices may yield additional benefit in preventing VTE compared with the use of either method alone. The use of elastic compression stockings is not recommended (Grade 2B). The risk of re-bleeding must be considered in patients with restricted mobility; if this risk is felt to be too great, mechanical prophylaxis with intermittent pneumatic compression devices can be utilized.

See Table 4.1 in Chapter 4 for a summary of the ACCP recommendations for the treatment of acute ischemic stroke and the prevention of VTE in patients with restricted mobility and acute intracranial hemorrhage. See Table 4.3 in Chapter 4 for the recommendations of the ACCP for antithrombotic therapy for stroke prevention after a noncardioembolic stroke or transient ischemic attack or after a primary intracranial hemorrhage.

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3. TREATMENT AND SECONDARY PROPHYLAXIS OF VENOUS THROMBOEMBOLISM

The mainstays of acute therapy for venous thromboembolism (VTE) include short-term therapy with low-molecular-weight heparin (LMWH), fondaparinux, or unfractionated heparin (UFH) and long-term therapy with warfarin (Table 3.1). Although these anticoagulants do not directly lyse or dissolve the clot, they stop clot propagation and allow the body's natural processes of clot lysis to remove it. Anticoagulant treatment reduces the risk of fatal pulmonary embolism (PE) and reduces VTE recurrence rates.[1]

When a practitioner has a high clinical index of suspicion for VTE, parenteral anticoagulant therapy should begin while the outcome of diagnostic tests is awaited (Grade 2C).[1] The ACCP recommends starting warfarin plus either intravenous UFH, fixed-dose subcutaneous UFH, subcutaneous UFH with dosage adjustment, LMWH, or fondaparinux at the time of diagnosis (all Grade 1B).[1]

LMWH or fondaparinux therapy is preferred over intravenous UFH (Grade 2C) or subcutaneous UFH (Grade 2B) because studies show that it results in lower incidences of thrombotic complications, major bleeding, and death (Grade 1C).[1] Considerations such as cost and familiarity should be taken into account when choosing between fondaparinux and LMWH. In the LTC setting, it is important to remember that LMWH and fondaparinux are retained in patients with renal impairment; however, this is not a concern with UFH.[1] The ACCP also recommends once-daily over twice-daily administration of LMWH in patients with acute deep venous thrombosis (DVT) of the leg when the once-daily regimen uses the same total daily dose as the twice-daily regimen.

For patients with severe renal failure (estimated creatinine clearance [CrCl] less than 30 ml/min), ACCP 2012 recommends a reduction in dose rather than standard doses (Grade 2C). For patients with body weight over 100 kg, the treatment dose of fondaparinux should be increased to 10 mg/day rather than the usual 7.5 mg/day.[2] Practitioners should follow manufacturers' guidelines for dosing in patients with severe renal impairment.

ACCP 2012 recommends that patients with DVT be encouraged with early ambulation over bed rest (Grade 2C). This recommendation contrasts with the common practice of enforcing several days of strict bed rest, which is intended to avoid embolization of thrombi in patients with DVT. Data do not support bed rest. The use of a compression bandage, combined with walking exercise in patients with acute DVT, is associated with a low incidence of recurrent and fatal PE.[1] Following acute DVT of the leg, patients should wear an elastic compression stocking (with a pressure of 30–40 mm Hg at the ankle) for 2 years after the acute episode (Grade 2B). Compression stockings are prescribed to reduce the incidence and severity of post-thrombotic syndrome.

Table 3.1 summarizes current ACCP recommendations for antithrombotic therapy for VTE treatment and secondary prophylaxis.

TABLE 3.1. ACCP Recommendations on Antithrombotic Treatment and Secondary Prophylaxis for Venous Thromboembolism

Note: * denotes agents with an FDA-approved indication for VTE treatment. All LMWHs, fondaparinux, and UFH are FDA approved for this indication.

Patient Category	Strong Recommendations	Weak Recommendations
Deep Venous Thrombosis		
Acute DVT of the Leg		
High clinical suspicion of DVT		Treat with parenteral anticoagulants while awaiting results of diagnostic tests (Grade 2C)
Intermediate clinical suspicion of DVT		Treat with parenteral anticoagulants if results of diagnostic tests are expected to be delayed more than 4 h (Grade 2C)
Low clinical suspicion of DVT		No treatment with parenteral anticoagulants provided results of diagnostic tests are expected within 24 h (Grade 2C)
Acute DVT	• Initial treatment with LMWH*, fondaparinux*, or UFH* for at least 5 days and until INR is 2.0 or above for at least 24 h (Grade 1B) • Initiate VKA therapy on same day parenteral anticoagulation is started (Grade 1B) • Patients who undergo thrombosis removal should receive same intensity and duration of anticoagulant therapy as patients who do not (Grade 1B) • Do not use IVCF in addition to anticoagulants (Grade 1B) • Long-term anticoagulant therapy recommended over stopping therapy after 1 wk (Grade 1B) • Reassess all patients receiving extended anticoagulant therapy at periodic intervals (e.g., annually) • All VKA-treated patients: maintain therapeutic INR range 2.0–3.0 (target 2.5) (Grade 1B) • Treat asymptomatic DVT identically to acute symptomatic DVT (Grade 1C)	• LMWH or fondaparinux preferred over IV UFH (Grade 2C) or subcut UFH (Grade 2B for LMWH, Grade 2C for fondaparinux) • In patients treated with LMWH, once-daily administration is preferred over twice-daily (Grade 2C) • Early ambulation preferred to initial bed rest (Grade 2C) • For patients without cancer, VKA preferred over LMWH for long-term therapy (Grade 2C) • For patients without cancer ***not*** treated with VKA, LMWH preferred over dabigatran or rivaroxaban (Grade 2C) • For extended therapy, continue same anticoagulant chosen for first 3 mo (Grade 2C) • Acute symptomatic DVT: use compression stockings (Grade 2B)
Acute isolated distal DVT of the leg	• No anticoagulation if thrombus does not extend (Grade 1B) • Anticoagulate if thrombus extends into proximal veins (Grade 1B) • DVT provoked by surgery or by a nonsurgical transient risk factor: treatment with anticoagulation for 3 mo recommended over treatment for 6–12 mo or extended therapy (both Grade 1B)	• Anticoagulate if thrombus extends but remains confined to distal veins (Grade 2C) • DVT provoked by surgery or nonsurgical transient risk factor: treatment with anticoagulation for 3 mo preferred over treatment for a shorter period (Grade 2C)

TABLE 3.1 Continued
ACCP Recommendations on Antithrombotic Treatment and Secondary Prophylaxis for Venous Thromboembolism
Note: * denotes agents with an FDA-approved indication for VTE treatment. All LMWHs, fondaparinux, and UFH are FDA approved for this indication.

Patient Category	Strong Recommendations	Weak Recommendations
Acute proximal DVT of the leg	• Provoked by surgery or nonsurgical transient risk factor: Treat with anticoagulation for 3 mo (Grade 1B)	• Anticoagulant therapy alone preferred to catheter-directed thrombolysis, systemic thrombolysis, or operative venous thrombectomy (all Grade 2C) • IVCF inserted as alternative to anticoagulation: use conventional course of anticoagulant therapy if bleeding risk resolves (Grade 2B)
Unprovoked DVT (isolated distal or proximal)	• Treat with anticoagulation for at least 3 mo (Grade 1B) • After 3 mo, evaluate risk-benefit ratio of extended therapy • First VTE, unprovoked DVT of leg, high bleeding risk: 3 mo of anticoagulant therapy (Grade 1B) • Second unprovoked VTE, low bleeding risk: extended anticoagulant therapy (Grade 1B)	• First VTE, unprovoked **proximal** DVT of leg, low or moderate bleeding risk: extended anticoagulant therapy (Grade 2B) • First VTE, unprovoked ***distal*** DVT of leg, low or moderate bleeding risk: 3 mo of anticoagulant therapy (Grade 2B) • Second unprovoked VTE, moderate bleeding risk: extended anticoagulant therapy (Grade 2B)
DVT with cancer	• Not high risk of bleeding: extended anticoagulant therapy (Grade 1B)	• High bleeding risk: extended anticoagulant therapy (Grade 2B) • LMWH (dalteparin*) preferred over VKA therapy (Grade 2B) • For patients not treated with LMWH, VKA preferred over dabigatran or rivaroxaban for long-term therapy (Grade 2B)
PTS of leg		• Trial of compression stockings (Grade 2C) • For severe PTS not adequately relieved by compression stockings, trial of IPC • Avoid venoactive medications (e.g., rutosides, defibrotide, hidrosmin) (Grade 2C)
SVT of lower limb		• For SVT of 5 cm or more, prophylactic dose of fondaparinux or LMWH for 45 days (Grade 2B) • Fondaparinux 2.5 mg/day preferred over LMWH (Grade 2C)
Acute Upper-Extremity DVT		
Axillary or more-proximal veins	• Parenteral anticoagulation (Grade 1B) • Same intensity and duration of anticoagulant therapy for patients who undergo thrombolysis as for patients who do not (Grade 1B)	• LMWH* or fondaparinux (in combination with warfarin*) preferred over IV UFH* (Grade 2C) or subcut UFH* (Grade 2B) • Anticoagulant therapy alone preferred over thrombolysis (Grade 2C) • Continue anticoagulation for at least 3 mo (Grade 2B)
UEDVT associated with central venous catheter	• No cancer, catheter removed: anticoagulation for 3 mo (Grade 1B) • Cancer, catheter not removed: continue anticoagulation as long as catheter remains in place (Grade 1C)	• Do not remove catheter if it is functional and needed (Grade 2C) • Cancer, catheter removed: anticoagulant therapy for 3 mo (Grade 2C) • No cancer, catheter not removed: continue anticoagulation as long as catheter remains in place (Grade 2C)

TABLE 3.1 Continued
ACCP Recommendations on Antithrombotic Treatment and Secondary Prophylaxis for Venous Thromboembolism
Note: * denotes agents with an FDA-approved indication for VTE treatment. All LMWHs, fondaparinux, and UFH are FDA approved for this indication.

Patient Category	Strong Recommendations	Weak Recommendations
UEDVT not associated with central venous catheter or cancer	Anticoagulation therapy for 3 mo (Grade 1B)	
Acute symptomatic UEDVT		Avoid using compression sleeves or venoactive medications (Grade 2C)
PTS of arm		• Trial of compression bandages or sleeves to reduce symptoms (Grade 2C) • Avoid treatment with venoactive medications (Grade 2C)
Splanchnic-vein thrombosis (portal, mesenteric, and/or splenic vein thromboses)	Symptomatic: anticoagulation (Grade 1B)	Asymptomatic: no anticoagulation (Grade 2C)
Hepatic vein thrombosis		No anticoagulation (Grade 2C)
Pulmonary Embolism		
High clinical suspicion of acute PE		Treat with parenteral anticoagulants while awaiting results of diagnostic tests (Grade 2C)
Intermediate clinical suspicion of acute PE		Treat with parenteral anticoagulants if results of diagnostic tests are expected to be delayed for more than 4 h (Grade 2C)
Low clinical suspicion of acute PE		No treatment with parenteral anticoagulants provided results of diagnostic tests are expected within 24 h (Grade 2C)
Acute PE	• Initial treatment with LMWH*, fondaparinux*, IV UFH*, or subcut UFH* (Grade 1B) • Initiate VKA on same day as parenteral therapy: continue for at least 5 days and until INR is 2.0 or above for at least 24 h (Grade 1B) • All VKA-treated patients: maintain therapeutic INR range 2.0–3.0 (target 2.5) (Grade 1B)	• LMWH or fondaparinux preferred over IV UFH (Grade 2C for LMWH, Grade 2B for fondaparinux) and subcut UFH (Grade 2B for LMWH, Grade 2B for fondaparinux) • Once-daily administration preferred in LMWH-treated patients (Grade 2C) • Long-term VKA therapy preferred over LMWH (Grade 2C) • If not treated with VKA, long-term LMWH therapy preferred over dabigatran or rivaroxaban (Grade 2C) • For extended therapy, continue same anticoagulant chosen for first 3 mo (Grade 2C) • Treat asymptomatic PE identically to symptomatic PE (Grade 2B) • When thrombolytic agents used ○ Short infusion time (e.g., 2 h) preferred (Grade 2C) ○ Administer through peripheral vein (Grade 2C)
Acute PE ***not*** associated with hypotension	Do ***not*** use systemic thrombolytic therapy (Grade 1C)	Low bleeding risk, high risk of developing hypotension: administer thrombolytic therapy (Grade 2C)
Acute PE associated with hypotension (e.g., systolic BP below 90 mm Hg)		Not high bleeding risk: systemic thrombolytic therapy (Grade 2C)
PE provoked by surgery	Treatment with anticoagulation for 3 mo recommended over all other durations of therapy (Grade 1B)	

TABLE 3.1 Continued
ACCP Recommendations on Antithrombotic Treatment and Secondary Prophylaxis for Venous Thromboembolism
Note: * denotes agents with an FDA-approved indication for VTE treatment. All LMWHs, fondaparinux, and UFH are FDA approved for this indication.

Patient Category	Strong Recommendations	Weak Recommendations
PE provoked by nonsurgical transient risk factor	High bleeding risk: treatment with anticoagulation for 3 mo recommended over all other durations of therapy (Grade 1B)	Low or moderate bleeding risk: treatment with anticoagulation for 3 mo preferred over extended therapy (Grade 2B)
Unprovoked PE	• Treat with anticoagulation for at least 3 mo (Grade 1B) • After 3 mo, evaluate risk-benefit ratio of extended therapy • First VTE, high bleeding risk: extended anticoagulant therapy (Grade 1B)	First VTE, low to moderate bleeding risk: extended anticoagulant therapy (Grade 2B)
PE and cancer	• Low to moderate bleeding risk: extended anticoagulant therapy (Grade 1B)	• High bleeding risk: extended anticoagulant therapy (Grade 2B) • LMWH preferred over VKA therapy (Grade 2B) • If not treated with LMWH, long-term VKA therapy preferred over dabigatran or rivaroxaban (Grade 2C)
IVCF	• Use IVCF in patients with contraindications to anticoagulation (Grade 1B) • Do ***not*** use of IVCF in patients treated with anticoagulants (Grade 1B)	If IVCF inserted as alternative to anticoagulation, use conventional course of anticoagulant therapy if bleeding risk resolves (Grade 2B)
CTPH	Extended anticoagulation therapy (Grade 1B)	Central disease, patient under care of experienced thromboendarterectomy team: pulmonary thromboendarterectomy (Grade 2C)

BP: blood pressure; CTPH: chronic thromboembolic pulmonary hypertension; DVT: deep venous thrombosis; INR: international normalized ratio; IPC: intermittent pneumatic compression; IV: intravenous; IVCF inferior vena cava filter; LMWH: low-molecular-weight heparin; PE: pulmonary embolism; PTS: post-thrombotic syndrome; subcut: subcutaneous; SVT: superficial vein thrombosis; UEDVT: upper-extremity deep vein thrombosis; UFH: unfractionated heparin, VKA: vitamin K antagonist (warfarin); VTE, venous thromboembolism.

Adapted from Kearon et al, Chest 2012[1]

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4. ANTITHROMBOTIC THERAPY FOR STROKE OR STROKE PREVENTION AND IN ATRIAL FIBRILLATION

Each year, more than 795,000 Americans experience a stroke. Twenty-four percent of strokes are recurrences.[1] Importantly, a recurrent stroke doubles the risk of death and other vascular complications[2] and increases the likelihood of stroke-related dementia.[3,4]

Six months after a stroke, one can expect that 50% of patients aged 65 or older will have some paralysis on one side of the body, 35% will experience symptoms of depression, 30% will require assistance with walking, 26% will be dependent in activities of daily living, 19% will have aphasia, and 26% will reside in long term care (LTC) facilities.[5] Many survivors require post-acute care for 6 months or more.[6]

Acute Stroke Care

In the setting of acute stroke, the role of antithrombotic therapy is to prevent acute stroke recurrence and to prevent deep venous thrombosis resulting from immobility. The recommendations of the ACCP on antithrombotic therapy for acute ischemic stroke are summarized in Table 4.1.

Treatment of Acute Ischemic Stroke

For patients with acute ischemic stroke, the ACCP recommends beginning aspirin therapy within 48 hours of acute stroke (once intracranial hemorrhage has been ruled out) at a dose of 160 to 325 mg/day, over no aspirin therapy (Grade 1A) and over parenteral anticoagulation (Grade 1A). This recommendation is based on evidence showing that acute therapy with aspirin has important benefits for mortality reduction and improved functional outcome compared with no aspirin therapy. Specifically, 1,000 patients with acute ischemic stroke treated with aspirin would be expected to experience nine fewer deaths, seven better functional outcomes at 30 days, four additional nonfatal extracranial bleeding events, and two more symptomatic intracranial hemorrhages.[7]

The starting dose of aspirin should be reduced to the maximum secondary prevention dose of 75 to100 mg/day after 1 to 2 weeks of acute therapy. Surprisingly, anticoagulation shows no net benefit over antiplatelet therapy in acute stroke, even among patients with atrial fibrillation (AF).

Venous Thromboembolism Prevention in Acute Stroke

For venous thromboembolism (VTE) prevention in patients with restricted mobility, the ACCP suggests prophylactic-dose heparin therapy begun within 48 hours after the stroke and continued until the end of the hospital stay or until the patient regains mobility (Grade 2B). Acceptable prophylactic regimens include unfractionated heparin (UFH; 10,000 to 15,000 units per day) or prophylactic-dose low-molecular-weight heparin (LMWH; 3000 to 6000 international units per day). Compared with patients receiving no heparin prophylaxis, 1,000 patients treated with heparin prophylaxis would be expected to experience 33 fewer DVTs and five fewer pulmonary embolisms (PEs), but suffer an additional three intracranial and two extracranial hemorrhages. LMWH is suggested over UFH (Grade 2B) because it can further reduce the number of VTEs in 1,000 patients by eight fewer PEs and seven fewer DVTs. This reduction benefit with LMWH occurs without any increase in bleed-

ing complications. The ACCP suggests against using elastic compression stockings (Grade 2B) because they have not been shown to decrease DVTs or PEs but have been shown to increase skin complications.[7]

For patients with acute intracerebral hemorrhage and restricted mobility, ACCP 2012 suggests starting subcutaneous UFH or LMWH between days 2 and 4 (Grade 2C). LMWH is preferred over UFH (Grade 2B). Practitioners may also choose intermittent pneumatic compression devices rather than subcutaneous UFH or LMWH (Grade 2C); however, elastic compression stockings should be avoided in patients with intracerebral hemorrhage who have restricted mobility (Grade 2B).[7]

TABLE 4.1. ACCP Recommendations on Antithrombotic Therapy for Acute Stroke
Note: * denotes agents with an FDA-approved indication for the recommended use.

	Strong Recommendations	Weak Recommendations
Treatment of Acute Ischemic Stroke		
Treatment of acute stroke or TIA	• Begin aspirin* therapy, 160–325 mg/day, within 48 h after stroke (Grade 1A) • Aspirin 160–325 mg/day recommended over therapeutic parenteral anticoagulation (Grade 1A)	Aspirin 75–100 mg/day after 1 to 2 weeks of acute aspirin therapy
Prevention of VTE in Acute Stroke		
Restricted mobility		• Prophylactic-dose subcut heparin (UFH*), or LMWH (enoxaparin*, dalteparin*), or IPCDs over no prophylaxis (Grade 2B) • Prophylactic-dose LMWH over prophylactic-dose UFH (Grade 2B) • Avoid elastic compression stockings (Grade 2B)
Acute intracranial hemorrhage and restricted mobility		• Prophylactic-dose subcut UFH or LMWH started on days 2 through 4, over no prophylaxis (Grade 2C) • Prophylactic-dose LMWH preferred over UFH (Grade 2B) • IPCDs preferred over no prophylaxis (Grade 2C) • Avoid elastic compression stockings (Grade 2B)

IPCD: intermittent pneumatic compression device; LMWH: low-molecular-weight heparin; subcut: subcutaneous; TIA: transient ischemic attack; UFH: unfractionated heparin; VTE: venous thromboembolism.

Adapted from Lansberg et al, 2012[7]

Prevention of Ischemic Stroke

Comprehensive stroke prevention includes risk factor reduction and antithrombotic treatment that is tailored to the pathophysiology of the patient's transient ischemic attack (TIA) or stroke (e.g., noncardioembolic, cardioembolic, or hemorrhagic). Modifiable stroke risk factors and approaches to stroke risk reduction are summarized in Table 4.2.

Age is the most important risk factor for stroke; the peak incidence of stroke occurs among people aged 80 years or older. With increasing age, the prognosis of stroke worsens, with higher chances of death and discharge to an LTC facility.[8,9] Despite the negative effects of advancing age on stroke outcome, those aged 80 or older derive the same magnitude of benefit from organized inpatient stroke care as do younger stroke patients.[10]

One study estimated that the expected 24% 5-year cumulative risk of recurrent stroke could be reduced by 80% if patients adopted dietary modifications, exercised, and received antihypertensive medications, aspirin, and a statin.[11] Multifactorial risk-factor reduction translates into a number needed to treat (NNT) of only 5, meaning that achieving preventive goals in five patients would prevent one stroke. Additional gains could be expected from smoking cessation, glycemic control, and appropriate use of anticoagulants for those with AF.[11]

TABLE 4.2. Modifiable Risk Factors for Transient Ischemic Attack and Stroke: Interventions, Treatment Goals, and Strategies for Monitoring Adverse Drug Effects

Note: See bottom of table for definitions of classes and levels of evidence.

Risk Factor	Intervention	Treatment Goal	Monitoring
Smoking Use of tobacco products	Provide counseling on the benefits of smoking cessation (IC)	• Smoking cessation • Stop use of tobacco products • Avoid secondhand smoke	Monitor smoking status
Alcohol consumption	Recommend avoidance of heavy alcohol consumption (more than 5 drinks/day) (IC)	Limit alcohol consumption to 2 drinks/day (men); 1 drink/day (women) (IIb, B)	Monitor alcohol consumption
Inactivity		Moderate-intensity physical exercise 30 minutes, 1 to 3 times weekly (IIb, C)	
Obesity Unhealthy diet	Weight loss as appropriate	DASH diet (salt restriction, diet rich in fruits, vegetables, and low-fat dairy products)[a]	Monitor weight
Hypertension	• Encourage lifestyle modification (IIa, C) • Antihypertensive treatment for those with hypertension (IA) • Antihypertensive treatment is reasonable for those without documented hypertension if considered appropriate for BP reduction (IIa, B) • Diuretics or combination of diuretic and ACEI are useful (IA) • Individualize BP medications based on patient characteristics and comorbidities (IIa, B)	• Individualize BP goals based on patient characteristics and comorbidities (IIa, B) • Benefit is seen with reductions of 10/5 mm Hg (IIa, B) • Normal BP is less than 120/80 (IIa, B)	• Check for symptoms of postural hypotension • Measure postural blood pressure, if appropriate • Perform appropriate laboratory testing as indicated (e.g., electrolytes, creatinine, BUN)
Diabetes	• Use existing guidelines for glycemic control (IB) • Use existing guidelines for blood pressure reduction (IB)	• Base goals for glucose control on comorbid conditions, presence of diabetic complications, and patient preferences (see AMDA clinical practice guideline on diabetes[b]) • Avoid lowering HbA1c to less than 6.5% in patients with a history of cardiovascular disease or vascular risk factors	Monitor according to medications used and goals of therapy

TABLE 4.2 Continued
Modifiable Risk Factors for Transient Ischemic Attack and Stroke: Interventions, Treatment Goals, and Strategies for Monitoring Adverse Drug Effects

Note: See bottom of table for definitions of classes and levels of evidence.

Risk Factor	Intervention	Treatment Goal	Monitoring
Hyperlipidemia	• For those without known CHD but with evidence of atherosclerosis or LDL higher than 100, prescribe intensive lipid-lowering therapy (IB) • For those with known CHD or hyperlipidemia, manage according to NCEP III (IA) • For those with low HDL consider treatment with niacin or gemfibrozil (IIb, B)	• Reduce LDL at least 50%, or target LDL to less than 70 (IIa, B) • Achieve NCEP III targets with lifestyle modifications, diet, and medications (IA)[c]	• Monitor according to medications used and goals of therapy • Check for muscle pain • Measure liver enzymes periodically • Monitor lipid profile periodically
Hormone replacement therapy	Estrogen with or without a progestin is not recommended (IIIA)	Discontinue estrogen if currently prescribed	
Noncardioembolic ischemic stroke/TIA	• Prescribe antiplatelet agents (IA) ○ Aspirin 50–325 mg/day(IA) ○ ERD-ASA 25 mg/200 mg twice daily (IB) ○ Clopidogrel 75 mg/day (IIa, B) • Do not combine aspirin and clopidogrel for routine stroke prevention (IIIA) • Do not prescribe oral anticoagulants rather than antiplatelet agents (IA) • If a stroke occurs while taking aspirin, no evidence supports increasing the aspirin dose, changing to an alternative antiplatelet agent or combining antiplatelet agents (IIb, C)		• Check for signs or symptoms of bleeding tendency (e.g., bruising, bleeding, petechiae) • Monitor laboratory tests as appropriate (e.g., fecal occult blood testing, hemoglobin, platelet count)
Atrial fibrillation	Consider long-term anticoagulation with warfarin (IA) (Weigh benefits and risks on the basis of risk factors and comorbid conditions)	INR 2.5 (range 2.0–3.0)	• Check for signs of bleeding • Consider testing periodically for fecal occult blood and hemoglobin • Monitor adequacy of anticoagulation
Atrial fibrillation, hemorrhagic contraindication to oral anticoagulation	• Prescribe aspirin alone (IA) • Do not prescribe aspirin plus clopidogrel (IIIB)		• Check for signs or symptoms of bleeding tendency (e.g., bruising, bleeding, petechiae) • Monitor laboratory tests as appropriate (e.g., fecal occult blood testing, hemoglobin, platelet count)

TABLE 4.2 Continued
Modifiable Risk Factors for Transient Ischemic Attack and Stroke: Interventions, Treatment Goals, and Strategies for Monitoring Adverse Drug Effects

Note: See bottom of table for definitions of classes and levels of evidence.

Risk Factor	Intervention	Treatment Goal	Monitoring
Mechanical cardiac valve	Long-term anticoagulation with warfarin (IB) (Weigh benefits and risks on the basis of risk factors and comorbid conditions)	INR 3.0 (range 2.5–3.5)	• Check for signs or symptoms of bleeding • Monitor laboratory tests as appropriate (e.g., fecal occult blood, hemoglobin) • Monitor adequacy of anticoagulation
Bioprosthetic cardiac valve	Consider warfarin (IIb, C)	INR 2.5 (range 2.0–3.0)	
Cardiomyopathy (EF 35% or less) with sinus rhythm	• Benefit of warfarin has not been established (IIb, B) • May consider warfarin (INR 2.0–3.0), aspirin 81 mg/day, clopidogrel 75 mg/day, or ERD-ASA 25 mg/75 mg twice daily to prevent recurrent ischemic events (IIb, B)		• Check for signs or symptoms of bleeding • Monitor laboratory tests as appropriate (e.g., fecal occult blood, hemoglobin) • Monitor adequacy of anticoagulation
Patent foramen ovale	• Antiplatelet therapy (IIa, B) • Data do not support equivalence or superiority of anticoagulants compared to aspirin (IIb, B) • Insufficient data exist regarding PFO closure (IIb, C)		

ACEI: angiotensin-converting enzyme inhibitor; BP: blood pressure; BUN: blood urea nitrogen; CHD: coronary heart disease; DASH: Dietary Approaches to Stop Hypertension; EF: ejection fraction; ERD-ASA: extended-release dipyridamole/aspirin; HbA1C: glycated hemoglobin; HDL: high-density lipoprotein; INR: international normalized ratio; LDL: low-density lipoprotein; NCEP: National Cholesterol Education Program; PFO: Patent foramen ovale; TIA: transient ischemic attack.

Source: Furie et al, 2011[12]
[a]Sacks et al, 2001[13]
[b]American Medical Directors Association. Managing Diabetes in the Long Term Care Setting. Clinical Practice Guideline. Columbia, MD.
[c]Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2011[14]

Definition of Classes and Levels of Evidence Used in American Heart Association Recommendations	
Class I	Conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment
Class IIa	The weight of evidence or opinion is in favor of the procedure or treatment
Class IIb	Usefulness/efficacy is less well established by evidence or opinion
Class III	Conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/effective and in some cases may be harmful
Therapeutic Recommendations	
Level of Evidence A	Data derived from multiple randomized clinical trials or meta-analyses
Level of Evidence B	Data derived from a single randomized trial or nonrandomized studies
Level of Evidence C	Consensus opinion of experts, case studies, or standard of care
Diagnostic Recommendations	
Level of Evidence A	Data derived from multiple prospective cohort studies using a reference standard applied by a masked evaluator
Level of Evidence B	Data derived from a single grade-A study, or one or more case-control studies, or studies using a reference standard

Source: Furie et al, 2011[12]

Antiplatelet Therapy to Prevent Thrombotic Stroke

An antiplatelet agent is indicated for all patients with a TIA or thrombotic stroke that is not caused by a cardioembolism.[12] A meta-analysis of studies comparing placebo to antiplatelet agents administered for an average of 29 months after a thrombotic stroke or TIA showed a 3.8% absolute reduction in the combined events of myocardial infarction (MI), stroke, and vascular death in patients who received antiplatelet therapy (NNT = 26).[15] The NNT was 40 for the prevention of one nonfatal stroke among patients receiving antiplatelet drugs. The adverse effects of antiplatelet therapy include a risk of one to two major extracranial bleeding events for every 1000 patients treated with antiplatelet therapy for 1 year.[15]

Aspirin

Aspirin (50 to 325 mg/day) is the most studied and least expensive antiplatelet agent for secondary stroke prevention.[12] The ACCP analysis estimates that if 1,000 patients with TIA or stroke took aspirin for 2 years, it would prevent five deaths, 25 strokes, and six myocardial infarctions (MIs) but cause seven major extracranial bleeding episodes.[7] Because of concerns that doses less than 75 mg/day may not reduce MI risk and evidence that bleeding risk begins to rise with doses over 100 mg, the ACCP recommends 75 to 100 mg/day for long-term stroke prevention in noncardioembolic ischemic stroke.[7]

Clopidogrel

Clopidogrel 75 mg/day is recommended for secondary prevention of noncardioembolic ischemic stroke (Grade 1A).[7] Clopidogrel is appropriate for patients who are allergic or sensitive to aspirin. For patients with a history of stroke or TIA, clopidogrel was not shown to be superior to aspirin for prevention of a subsequent stroke, MI, or death resulting from another vascular cause.[16] The ACCP analysis differed from this trial slightly and suggested that if 1,000 patients received clopidogrel rather than aspirin, the benefit would be two fewer MIs, but with no difference in mortality, stroke, or bleeding. Thus, on the basis of this evidence, the ACCP recommends clopidogrel over aspirin (Grade 2B).

Clopidogrel Plus Aspirin

Treatment with aspirin, clopidogrel, extended-release dipyridamole/aspirin, or cilostazol is recommended over the combination of clopidogrel plus aspirin (Grade 1B). Clopidogrel plus aspirin is not superior to clopidogrel alone for stroke prevention and the combination regimen raises the incidence of serious gastrointestinal bleeding.[17] Combined therapy with clopidogrel and aspirin may be appropriate for patients with a stroke or TIA and recent balloon angioplasty or an intracoronary stent.[18,19] Thus, if a patient with a TIA or stroke is taking both clopidogrel and aspirin for coronary artery disease, it is reasonable to continue combination therapy according to the cardiac indication.

Extended-Release Dipyridamole/Aspirin

ACCP 2012 recommends extended-release dipyridamole/aspirin (ERD-ASA; 25/200 mg twice daily) over no anticoagulant therapy for secondary prevention of noncardioembolic ischemic stroke (Grade 1A).[7] This treatment regimen is more ex-

pensive than aspirin alone but was superior to aspirin alone for stroke prevention in one randomized controlled trial.[20] The ACCP projects that for 1000 patients taking ERD-ASA rather than aspirin alone for 2 years, one could expect 24 fewer strokes to occur, with no differences in mortality or bleeding. Thus, the ACCP suggests the use of ERD-ASA preferentially over aspirin (Grade 2B) or cilostazol (Grade 2C).[7]

Table 4.3 summarizes current ACCP recommendations on antithrombotic therapy for stroke prevention.

TABLE 4.3. ACCP Recommendations on Antithrombotic Therapy for Stroke Prevention
Note: * denotes agents with an FDA-approved indication for the recommended use.

Patient Category	Recommendations	Suggestions/Comments
Noncardioembolic stroke or TIA	• Aspirin* 75–100 mg/day, over no therapy (Grade 1A) • Clopidogrel* 75 mg/day (Grade 1A) • ERD-ASA* 25/200 mg twice daily (Grade 1A) • Cilostazol 100 mg twice daily (Grade 1A) • Recommend clopidogrel ***or*** ERD-ASA over aspirin (Grade 2B) or cilostazol (Grade 2C). Aspirin, clopidogrel, ERD-ASA, and cilostazol preferred over each of following: ○ No antiplatelet therapy (Grade 1A) ○ Oral anticoagulants (Grade 1B) ○ Clopidogrel plus aspirin (Grade 1B) ○ Triflusal (Grade 2B) *Note: As of July 2012, triflusal is not FDA approved for any indication in the United States.*	Oral anticoagulation associated with higher all-cause mortality and major bleeding events
Primary intracranial hemorrhage	Recommend against long-term use of antithrombotic therapy for prevention of ischemic stroke (Grade 2C)	Antithrombotic therapy may be appropriate if high risk for recurrence (e.g., mechanical heart valve, CHADS score 4 or more)

ERD-ASA: extended release/dipyridamole/aspirin; *TIA:* transient ischemic attack.

Adapted from Lansberg et al, 2012[7]

Atrial Fibrillation

AF is the most sustainable arrhythmia in adults and is responsible for 15% of ischemic strokes.[21] Persistent AF and paroxysmal AF both impart the same increased risk for cardioembolic ischemic stroke in the presence of AF. In patients with AF who have risk factors for stroke, success in controlling or eliminating AF does not eliminate the need for long-term anticoagulant therapy.[22,23] Anticoagulation with an oral vitamin K antagonist (VKA) such as warfarin decreases the risk of stroke by approximately 65%. In addition, if the international normalized ratio (INR) is in the therapeutic range and a stroke occurs, it is likely to be less severe.[24] Studies estimate an NNT of 32 for stroke prevention using a VKA versus placebo.[21]

Because of the serious and potentially lethal adverse effects of both choosing and foregoing warfarin therapy, the practitioner should engage in a shared decision-making process with the patient and family to determine whether to use warfarin

for stroke prevention. All recommendations for prophylactic warfarin use in LTC patients assume that the practitioner has access to a system for monitoring INR and keeping it in the ideal range and has taken into consideration the patient's bleeding risk, functional status, and prognosis. Appendixes 5 to 10 present examples of guidelines and policies for the initiation, dosage adjustment, and monitoring of warfarin therapy.

The target INR for stroke prevention in patients with AF is 2.5 (range, 2.0 to 3.0).[18] Studies show that the preventive efficacy of warfarin is ideal when the INR is at 2.0, with no further risk reduction apparent for INRs above 2.0.[25] Conversely, warfarin maintained at an INR below 2.0 does not decrease bleeding risk when compared with INRs of 2.0 to 3.0,[26] but does increase stroke risk.[25] Stroke risk rises dramatically when the INR is at or below 1.8; it doubles when the INR is at or below 1.7 and triples when the INR is at or below 1.5.[25]

Aspirin may be more efficacious for AF patients with hypertension or diabetes and for reduction of noncardioembolic versus cardioembolic ischemic stroke. Aspirin appears to prevent nondisabling strokes more than disabling strokes. Thus, the greater the risk of disabling cardioembolic stroke in a population of patients with AF, the less protection is afforded by aspirin.[27]

Role of New Oral Anticoagulants

Dabigatran, rivaroxaban, and apixaban have all been tested for prevention of stroke and AF. In the major trials of these agents, intracranial hemorrhage rates, including hemorrhagic stroke and other intracranial bleeding events, were lower among patients taking the new oral anticoagulants compared with warfarin. Thus, for patients with nonrheumatic AF, recommendations for VKA therapy include recommendations for the use of dabigatran. The recommendation for dabigatran therapy presumes that the 150-mg twice-daily dose will be used. It is important to remember that the 75-mg twice-daily dose recommended for patients with creatinine clearance of 15 to 30 ml/min has no direct evidence from randomized control trials in AF to confirm its efficacy. Rather, this dose was based on pharmacokinetic data to suggest a safe dose in renal insufficiency.

Antithrombotic Therapy for Patients With Atrial Fibrillation

Table 4.4 summarizes current ACCP recommendations on antithrombotic therapy for the management of AF.

The ACCP outlined the methods they used to assess the risks and benefits of the options available for antithrombotic treatment for AF. They began with an expert panel's assessment that patients would rate a nonfatal stroke three times as aversely as a nonfatal gastrointestinal bleeding event. On the basis of this utility estimate, the ACCP recommended only those treatments likely to prevent at least three times more nonfatal strokes than the expected number of nonfatal bleeding events.[18]

In addition, their assessment of the data was that for long-term stroke prevention in AF, no differences in all-cause mortality exist among the current options for antithrombotic treatment. Importantly, all antithrombotic treatment choices are preferable to no therapy for those patients choosing to reduce the risk of stroke from AF.[18]

When addressing stroke risk for patients with AF, the ACCP suggests using the CHADS-2 score but points out that it has a relatively low positive predictive value. One potential limitation of the CHADS-2 score is that it does not take into account

the fact that stroke risk rises continuously with increasing age. Moreover, although the ACCP recommendations for anticoagulation are based on CHADS-2 scores, their risk-benefit assessments assign different, and lower, absolute rates of nonfatal stroke to CHADS-2 scores than those assigned by the original developers of the CHADS-2 score (Table 4.5). The ACCP estimates are derived from recent studies, but they have not been compared with the original CHADS-2 estimates in prospective studies.

When calculating bleeding risk related to VKA therapy, the ACCP panel combined data from multiple studies to estimate that the median rate of bleeding on VKA therapy was 1.3% per year, an increase of 0.8% over the baseline risk of nonfatal major extracranial bleeding without VKA therapy of 0.5% per year. They also estimated that 50% of hemorrhagic strokes, 25% of ischemic strokes, and approximately 15% of extracranial bleeding events result in death.[18] The ACCP panel estimated that VKA therapy reduces the risk of nonfatal stroke by two-thirds and the risk of death by one-fourth compared with no therapy.

It is important to remember that atrial flutter and paroxysmal atrial fibrillation carry the same stroke risk as does AF; thus, the recommendations for oral anticoagulation therapy are the same as for AF. Of equal importance are trial data confirming that the benefits of oral anticoagulant therapy are similar among patients regardless of whether they receive treatment to control their rhythm, such as antiarrhythmic medication or catheter ablation.

TABLE 4.4. ACCP Recommendations for the Management of Atrial Fibrillation

Note: * denotes agents with an FDA-approved indication for the recommended use.

Patient Category	Strong Recommendations	Weak Recommendations
AF, including paroxysmal AF		
CHADS-2 = 0 (Low risk of stroke)		• No antithrombotic therapy (Grade 2B) • Multiple non-CHADS-2 risk factors for stroke may favor patient choice of antithrombotic therapy • If patient chooses antithrombotic therapy, aspirin 75–325 mg/day (Grade 2B), rather than oral anticoagulation (Grade 2B) or aspirin plus clopidogrel (Grade 2B)
CHADS-2 = 1 (Intermediate risk of stroke)	• Oral anticoagulation (warfarin*) rather than no therapy (Grade 1B)	• Oral anticoagulation rather than aspirin* 75–325 mg/day (Grade 2B) or combination therapy with aspirin and clopidogrel (Grade 2B) • Aspirin plus clopidogrel* over aspirin alone for patients unwilling or unable to take oral anticoagulants (Grade 2B) • Oral anticoagulation choice: dabigatran* 150 mg twice daily over VKA (Grade 2B) • Reduce dabigatran dose to 75 mg twice daily if CrCl 15–30 ml/min
CHADS-2 = 2 or more (High risk of stroke)	• Oral anticoagulation (warfarin*) rather than no therapy (Grade 1A), • Oral anticoagulation rather than aspirin (Grade 1B), or combination therapy with aspirin and clopidogrel (Grade 1B) • Aspirin* plus clopidogrel*, rather than aspirin alone, for patients unwilling or unable to take oral anticoagulants (Grade 1B)	• Educate patients that antiplatelet therapy is inferior to oral anticoagulant treatment for stroke prevention • Oral anticoagulation choice: dabigatran* 150 mg twice daily over VKA (warfarin*) (Grade 2B) • Reduce dabigatran dose to 75 mg twice daily if CrCl 15–30 ml/min
AF with PCI, with or without recent ACS		
CHADS-2 = 0 or 1 1st 12 mo after BMS or DES		Dual antiplatelet therapy rather than triple therapy (Grade 2C)
CHADS-2 = 0 or 1 12 mo after BMS or DES		VKA alone (warfarin*) over VKA plus aspirin (Grade 2C)
CHADS-2 = 2 or more 1st mo after BMS 1st 3–6 mo after sirolimus, zotarolimus, or everolimus DES 1–6 mo after paclitaxel DES		• Triple therapy VKA (warfarin*), aspirin*, and clopidogrel* (Grade 2C) • May consider 12 mo of triple therapy if high risk for late stent thrombosis

TABLE 4.4 Continued
ACCP Recommendations for the Management of Atrial Fibrillation
Note: * denotes agents with an FDA-approved indication for the recommended use.

Patient Category	Strong Recommendations	Weak Recommendations
CHADS-2 = 2 or more 2–12 mo after BMS 4–12 mo after sirolimus, zotarolimus, or everolimus DES 6–12 mo after paclitaxel DES		After initial triple therapy, VKA plus single antiplatelet drug (Grade 2C)
CHADS-2 = 2 or more 12 mo after intracoronary stent placement		VKA alone over VKA (warfarin*) plus aspirin* (Grade 2C)
AF with ACS, no intracoronary stent		
CHADS-2 = 0		• Dual antiplatelet therapy rather than VKA therapy plus a single antiplatelet therapy (Grade 2C) • Dual antiplatelet therapy rather than triple therapy (warfarin plus dual antiplatelet therapy) (Grade 2C) • After 12 mo, VKA alone over VKA plus aspirin (Grade 2C) • Patients may choose VKA plus single antiplatelet therapy based on concern for avoiding stroke, additional stroke risk factors, and considerations of bleeding risk
CHADS-2 = 1 or more		• VKA therapy plus single antiplatelet therapy for 12 mo (Grade 2C) • After 12 mo, VKA alone over VKA plus aspirin (Grade 2C)
Other		
AF and mitral stenosis	• VKA (warfarin*) over no therapy (Grade 1B) • VKA over aspirin (75–325 mg/day) or combination therapy with aspirin and clopidogrel (all Grade 1B) • Aspirin plus clopidogrel over aspirin alone for patients unwilling or unable to take VKA (Grade 1B)	
AF and stable CAD		VKA alone (warfarin*) over VKA plus aspirin (Grade 2C)
AF managed with rhythm control strategy (pharmacologic or catheter ablation)		Follow general risk-based recommendations for patients with AF, including paroxysmal AF, regardless of apparent persistence of NSR (Grade 2C)
Atrial flutter		Follow same risk-based recommendations as for AF

ACS: acute coronary syndrome; AF: atrial fibrillation; BMS: bare metal stent; CAD: coronary artery disease; CHADS-2: Congestive heart failure, Hypertension, Age, Diabetes, prior Stroke; CrCl: creatinine clearance; DES: drug-eluting stent; NSR: normal sinus rhythm; PCI: percutaneous coronary intervention; VKA: vitamin K antagonist.

Adapted from You et al, 2012[18]

TABLE 4.5 Risk of Stroke for Patients With Atrial Fibrillation (CHADS-2)

Calculation of CHADS-2 score:

- Add 1 point for each of the following conditions:
  - Moderately or severely impaired LV systolic function and/or CHF
  - Hypertension
  - Aged 75 or older
  - Diabetes mellitus
- Add 2 points for a prior stroke or TIA

Risk estimates of original developers of CHADS-2: (Gage et al, 2001[28])

CHADS-2 Score	Adjusted stroke rate* [95% confidence interval]
0	1.9 [1.2–3.0]
1	2.8 [2.0–3.8]
2	4.0 [3.1–5.1]
3	5.9 [4.6–7.3]
4	8.5 [6.3–11.1]
5	12.5 [8.2–17.5]
6	18.2 [10.5–27.4]

* Expected stroke rate per 100 person-years. The model assumed that patients did not take aspirin.

ACCP 2012 risk estimates: (You et al, 2012[18])

CHADS-2 Score	Stroke Rate, %
0	0.8
1	2.2
2	4.5
3–6	9.6

CHF: congestive heart failure; LV: left ventricular; TIA: transient ischemic attack.

Aspirin Monotherapy Versus Vitamin K Antagonist Therapy

Compared with no therapy, aspirin may reduce the relative risk of nonfatal stroke by 21% and increase by 50% to 60% the relative risk of major extracranial bleeding. High-quality evidence shows that VKA therapy is superior to aspirin, consistently decreasing the stroke rate by 50% (3, 9, 19, and 40/1,000 fewer strokes for CHADS-2 scores of 0, 1, 2, and 3 to 6, respectively). Aspirin therapy would be expected to result in nonfatal bleeding rates of 8/1,000, compared with 11/1,000 with VKA therapy. Surprisingly, no important difference in death rates exists between the two treatments.

Aspirin Plus Clopidogrel Versus Aspirin Alone

Clopidogrel plus aspirin was more effective than aspirin alone in reducing nonfatal stroke in patients with AF (2, 5, 10, and 21/1,000 fewer strokes for CHADS-2 scores of 0, 1, 2, and 3 to 6, respectively). Unfortunately, the combination therapy resulted in a rate of 12/1,000 nonfatal major extracranial bleeds compared with 8/1,000 for aspirin alone.

Oral Anticoagulation Risk-Benefit According to Stroke Risk

For patients with a CHADS-2 score of 0, ACCP 2012 suggests no antithrombotic therapy (Grade 2B). This is based on the fact that, when compared with no treatment, VKA therapy can be expected to prevent five nonfatal strokes per 1,000 patients, but will cause eight additional nonfatal major bleeding events. The benefit of aspirin in this group is low, with an estimated NNT of 500 to prevent one stroke.

For patients with a CHADS-2 score of 1, oral anticoagulation therapy is recommended over no therapy (Grade 1B), aspirin monotherapy (Grade 2B), and aspirin combined with clopidogrel (Grade 2B). Compared with no therapy, 1,000 patients taking VKA therapy would be expected to experience 15 fewer deaths, 15 fewer nonfatal strokes, and suffer eight more nonfatal extracranial bleeds. Compared with aspirin monotherapy, 1,000 patients on VKA therapy would have no reduction in death rate but would have nine fewer nonfatal strokes offset by three additional nonfatal major bleeding events. When compared with aspirin plus clopidogrel, 1,000 patients on VKA therapy would see no reduction in mortality rate and experience a statistically similar rate of major extracranial bleeding episodes, but would expect six fewer nonfatal strokes.

For patients with a CHADS-2 score of 2 or higher, VKA is recommended over no therapy (Grade 1A). For this group, the benefits of VKA therapy are more dramatic, producing 15 fewer deaths and 30 fewer strokes per 1,000 patients compared with no therapy. VKA therapy is superior to aspirin monotherapy (Grade 1B), with 19 fewer nonfatal strokes but three more extracranial bleeding events. Compared with aspirin plus clopidogrel, 1,000 patients receiving VKA treatment would have 11 fewer strokes, with no statistically significant difference in death or bleeding rates. Accordingly, oral anticoagulation is preferred over aspirin plus clopidogrel (Grade 1B). For patients unable or unwilling to take oral anticoagulants, aspirin plus clopidogrel is preferred over aspirin alone (Grade 1B). The ACCP panel specifically recommends informing patients that antiplatelet therapy is inferior to oral anticoagulant therapy for stroke prevention when the CHADS-2 score is 2 or more.

Atrial Fibrillation in Patients With Coronary Artery Disease

In one large study of patients with AF, 30% also had coronary artery disease.[29] The treatment of patients with both coronary artery disease and AF is complicated by the increased risk of bleeding when combining oral anticoagulants with aspirin and other antiplatelet agents.

The current ACCP guideline makes different recommendations based on whether the patient with AF has stable coronary artery disease, acute coronary syndrome (ACS), or an intracoronary artery stent. Patients with stable coronary artery disease may or may not have angina, but may not have had a percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG), or hospitalization for acute coronary syndrome within the past year. The ACCP defines ACS as unstable angina, non-ST segment elevation MI (NSTEMI), or ST segment elevation MI in the prior year.

Atrial Fibrillation with Stable Coronary Artery Disease

Studies of treatment with aspirin and VKA therapy (combination therapy) have shown nearly twice as many major increased bleeding events without any reduction

in death rate or stroke prevention.[30-33] Thus, the ACCP recommends that patients with AF and stable coronary artery disease use adjusted-dose VKA therapy rather than the combination of adjusted-dose VKA therapy and aspirin (Grade 2C).

Patients With Atrial Fibrillation and Acute Coronary Syndrome Without Stent Placement

Usually, after ACS without a stent, a patient will receive dual antiplatelet therapy for 12 months. For patients with AF and ACS, triple therapy with VKA plus two antiplatelet agents only provides a net clinical benefit over dual antiplatelet therapy for those with a CHADS-2 score of 2 or higher. No direct data allow comparison of triple therapy with dual therapy consisting of warfarin combined with a single antiplatelet agent for patients with AF and ACS. Evidence suggests that for ACS uncomplicated by AF, warfarin plus aspirin is at least as effective as dual antiplatelet therapy. Thus, for higher-risk patients with a CHADS-2 score of 1 or more, VKA plus a single antiplatelet agent is recommended over dual antiplatelet therapy or triple therapy for the 12 months following ACS (Grade 2C). For patients with a CHADS-2 score of 0, the ACCP suggests dual antiplatelet therapy for 12 months rather than VKA plus a single antiplatelet agent (Grade 2C). After 12 months, VKA alone is preferred over combination therapy (Grade 2C).

Atrial Fibrillation Following Intracoronary Stent Placement

After intracoronary stent placement, it is typical for patients to receive dual antiplatelet therapy with aspirin and clopidogrel. Dual antiplatelet therapy is necessary to prevent stent thrombosis, which has a mortality rate of nearly 50%.

The optimal treatment of patients requiring anticoagulation with VKA for AF who also have coronary artery disease is problematic owing to the lack of randomized controlled trials to answer this question. No direct evidence gives guidance on how long patients with AF should receive triple therapy (i.e., warfarin plus dual antiplatelet therapy). The ACCP panel sought a balance between the risks associated with AF (stroke, VTE, death), the risk of recurrent MI and/or stent thrombosis, and bleeding risk. They noted that for patients with risk factors for late stent thrombosis (diabetes, long intracoronary lesions, narrowed target vessels, or ACS at the time of PCI), it may be reasonable to continue triple therapy for 12 months after PCI. This choice implies a greater emphasis on avoiding MI or stent thrombosis than on avoiding bleeding episodes. After the initial 12 month period, patients should follow treatment recommendations for AF with stable coronary artery disease and take VKA alone rather than combination therapy (Grade 2C).[18]

Duration of triple therapy (warfarin plus dual antiplatelet therapy) varies according to the type of stent. Bare-metal stents (BMS) require 4 weeks of dual therapy; drug-eluting stents (DES) show delayed stent endothelialization and require a longer duration of dual antiplatelet therapy. Some DES use sirolimus, zotarolimus, or everolimus and are known as the '-olimus' group of stents. A DES may also use paclitaxel, which is referred to as a '-taxel' stent. The -olimus stents require warfarin plus 3 months of dual antiplatelet therapy, whereas -taxel stents require warfarin plus 6 months of dual antiplatelet therapy.[19]

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5. ANTITHROMBOTIC THERAPY IN CARDIOVASCULAR DISEASE

Coronary Artery Disease[1]

Because thrombosis is a key component of both the pathogenesis and complications of the atherosclerotic process in coronary artery disease, both antiplatelet and anticoagulant therapies are mainstays in the management of this condition. Dual antiplatelet therapy with aspirin and clopidogrel is increasingly common. The duration of dual antiplatelet therapy depends on the initial indication (e.g., acute coronary syndrome [ACS] with ST elevation, percutaneous coronary intervention with a bare metal or drug-eluting stent).

In the Clopidogrel in Unstable Angina to Prevent Recurrent Events trial (CURE), patients with acute coronary syndrome receiving aspirin who received clopidogrel pretreatment followed by long term clopidogrel therapy had fewer major cardiovascular events than patients treated with placebo.[2]

The current ACCP recommendations for antithrombotic therapy in coronary artery disease are summarized in Table 5.1.

TABLE 5.1. Antithrombotic (Antiplatelet, Anticoagulant) Therapy Post Myocardial Infarction and Post Acute Coronary Syndrome

Note: * denotes agents with an FDA-approved indication for the recommended use. (Antiplatelet agents are generally indicated for thromboprophlaxis.)

Patient Category	Recommendations	Suggestions/Comments
Established CAD		
1 y post ACS, prior revascularization, coronary stenoses over 50% by coronary angiogram, ***and/or*** evidence for cardiac ischemia on diagnostic testing (including patients after first year post-ACS and/or with prior CABG)	• Long-term single antiplatelet therapy with aspirin* 75–100 mg/day ***or*** clopidogrel* 75 mg/day over no antiplatelet therapy (Grade 1A)	Single over dual antiplatelet therapy with aspirin plus clopidogrel (Grade 2B)
Less than 1 y post ACS, no PCI	Dual antiplatelet therapy (ticagrelor* 90 mg twice daily plus aspirin* 75–100 mg/day; clopidogrel* 75 mg/day plus aspirin* 75–100 mg/day; ***or*** prasugrel* 10 mg/day plus aspirin 75–100 mg/day) over single antiplatelet therapy (Grade 1B)	Ticagrelor 90 mg daily plus aspirin 75–100 mg/day over clopidogrel 75 mg/day plus low-dose aspirin (Grade 2B)
Less than 1 y post ACS, PCI with stent placement	Dual antiplatelet therapy (ticagrelor* 90 mg twice daily plus aspirin 75-100 mg/day; clopidogrel* 75 mg/day plus aspirin* 75–100 mg/day; ***or*** prasugrel* 10 mg/day plus aspirin 75–100 mg/day) over single antiplatelet therapy (Grade 1B)	Ticagrelor 90 mg twice daily plus aspirin 75–100 mg/day over clopidogrel 75 mg/day plus aspirin 75–100 mg/day (Grade 2B)
Elective PCI		
Elective BMS or DES placement	• Aspirin 75–100 mg/day plus clopidogrel* 75 mg/day alone rather than cilostazol in addition to these drugs (Grade 1B) • Aspirin 75–100 mg/day ***or*** clopidogrel 75 mg/day as part of dual antiplatelet therapy rather than using either drug with cilostazol (Grade 1B)	Cilostazol 100 mg twice daily as substitute for either aspirin 75–100 mg/day or clopidogrel 75 mg/day as part of a dual antiplatelet regimen in patients with allergy or intolerance to either drug class (Grade 2C)
BMS placement		
First mo	Dual antiplatelet therapy (aspirin* 75–325 mg/day plus clopidogrel* 75 mg/day) over single antiplatelet therapy (Grade 1A)	
Next 11 mo		Dual antiplatelet therapy (aspirin 75–100 mg/day plus clopidogrel 75 mg/day) over single antiplatelet therapy (Grade 2C)
After 12 mo	Single antiplatelet therapy over continuation of dual antiplatelet therapy (Grade 1B)	

TABLE 5.1 Continued
Antithrombotic (Antiplatelet, Anticoagulant) Therapy Post Myocardial Infarction and Post Acute Coronary Syndrome
Note: * denotes agents with an FDA-approved indication for the recommended use. (Antiplatelet agents are generally indicated for thromboprophlaxis.)

Patient Category	Recommendations	Suggestions/Comments
DES placement		
First 3–6 mo	Dual antiplatelet therapy (aspirin* 75–325 mg/day plus clopidogrel* 75 mg/day) over single antiplatelet therapy (Grade 1A) **Note:** Absolute minimum duration will vary based on stent type (in general, 3 mo for -limus stents, 6 mo for -taxel stents)	
After 3–6 mo		Continue dual antiplatelet therapy (aspirin* 75–100 mg/day plus clopidogrel* 75 mg/day) until 12 mo over single antiplatelet therapy (Grade 2C)
After 12 mo	• Single antiplatelet therapy over continuation of dual antiplatelet therapy (Grade 1B) • Thereafter, single antiplatelet therapy (aspirin* 75–100 mg/day ***or*** clopidogrel* 75 mg/day) over no antiplatelet therapy (Grade 1A)	Single over dual antiplatelet therapy with aspirin plus clopidogrel (Grade 2B)
CAD, elective PCI, no stent placement		
First mo		• Dual antiplatelet therapy (aspirin* 75–325 mg/day plus clopidogrel* 75 mg/day) over single antiplatelet therapy (Grade 2C) • Single over dual antiplatelet therapy with aspirin plus clopidogrel (Grade 2B)
After first mo	Single antiplatelet therapy (long-term aspirin* 75–100 mg/day ***or*** clopidogrel* 75 mg/day) over no antiplatelet therapy (Grade 1A)	
Systolic LV dysfunction		
No established CAD, no LV thrombus		No antiplatelet therapy or warfarin (Grade 2C)
No established CAD, identified acute LV thrombus		Moderate-intensity warfarin (INR 2.0–3.0) for at least 3 mo (Grade 2C)
Established CAD	Per recommendations for established CAD: long-term single antiplatelet therapy with aspirin* 75–100 mg/day ***or*** clopidogrel* 75 mg/day over no antiplatelet therapy (Grade 1A)	Single over dual antiplatelet therapy with aspirin plus clopidogrel (Grade 2B)
Anterior MI and LV thrombus or high risk for LV thrombus (EF less than 40%, antero-apical wall motion abnormality)		
No stenting		
First 3 mo	Warfarin* (INR 2.0–3.0) plus aspirin* 75–100 mg/day over single antiplatelet therapy or dual antiplatelet therapy (Grade 1B)	

TABLE 5.1 Continued
Antithrombotic (Antiplatelet, Anticoagulant) Therapy Post Myocardial Infarction and Post Acute Coronary Syndrome
Note: * denotes agents with an FDA-approved indication for the recommended use. (Antiplatelet agents are generally indicated for thromboprophlaxis.)

Patient Category	Recommendations	Suggestions/Comments
3–12 mo	Discontinue warfarin, continue dual antiplatelet therapy for up to 12 mo per recommendations for ACS	
After 12 mo	Single antiplatelet therapy per recommendations for established CAD (long term single antiplatelet therapy with aspirin 75–100 mg/day ***or*** clopidogrel 75 mg/day over no antiplatelet therapy) (Grade 1A)	Single over dual antiplatelet therapy with aspirin plus clopidogrel (Grade 2B)
BMS placement		
First mo		Triple therapy (warfarin* [INR 2.0–3.0], aspirin* 75–100 mg/day, clopidogrel* 75 mg/day) for 1 mo over dual antiplatelet therapy (Grade 2C)
2nd and 3rd mo		Warfarin (INR 2.0–3.0) and single antiplatelet therapy over alternative regimens and alternative time frames for warfarin use (Grade 2C)
3–12 mo	Discontinue warfarin, use dual antiplatelet therapy for up to 12 mo per recommendations for ACS	
After 12 mo	Antiplatelet therapy per recommendations for established CAD	
DES placement		
3–6 mo		Triple therapy (warfarin* [INR 2.0–3.0], aspirin* 75–100 mg/day, clopidogrel* 75 mg/day) over alternative regimens and alternative durations of warfarin therapy (Grade 2C)
6–12 mo	Discontinue warfarin, continue dual antiplatelet therapy for up to 12 mo per recommendations for ACS	
After 12 mo	Antiplatelet therapy per recommendations for established CAD	

ACS: acute coronary syndrome; BMS: bare-metal stent; CAD: coronary artery disease; CABG: coronary artery bypass graft; DES: drug-eluting stent; EF: ejection fraction; INR: international normalized ratio; LV: left ventricular; MI: myocardial infarction; PCI: percutaneous coronary intervention.

Adapted from: Vandvik et al, 2012[1]

Peripheral Arterial Occlusive Disease[3]

Peripheral arterial occlusive disease (peripheral artery disease [PAD]) is a significant cause of hospital admission and an important predictor of cardiovascular and stroke mortality. Almost all patients with asymptomatic PAD have occult coronary or cerebrovascular disease. Thus, it is important to address modifiable cardiovascular risk factors (e.g., chronic kidney disease, diabetes, hyperlipidemia, hypertension, inactivity, smoking) in addition to prescribing appropriate antithrombotic therapy for patients with PAD. Disease progression is greatest in patients who are current or prior smokers or who have chronic renal insufficiency, diabetes, low ankle-to-brachial pressure indices, or multilevel arterial involvement.

The 2012 ACCP guidelines state that aspirin slightly reduces total mortality regardless of cardiovascular risk profile if taken over 10 years. In patients with moderate-to-high risk of cardiovascular events, the reduction in myocardial infarction is almost off set by an increase in major bleeds. Daily aspirin therapy (75–100 mg) is recommended for patients with asymptomatic peripheral artery disease.

Two options, either aspirin 75–100 mg/day or clopidogrel 75 mg/day, are available for secondary prevention in patients with symptomatic PAD (Grade 1A).

Current ACCP recommendations for the management of PAD are summarized in Table 5.2.

Chronic Limb Ischemia[3]

ACCP 2012 suggests that patients with symptomatic peripheral artery disease who have pain at rest but are not candidates for surgical revascularization should receive aspirin 75–100 mg/day or clopidogrel 75 mg/day (Grade 2C) in combination with a prostanoid.

TABLE 5.2. ACCP Recommendations for the Management of Peripheral Arterial Occlusive Disease

Note: * denotes agents with an FDA-approved indication for the recommended use. (Antiplatelet agents are generally indicated for thromboprophlaxis.)

Patient Category	Recommendations	Suggestions
Peripheral artery disease		
Asymptomatic PAD	Aspirin* 75–100 mg/day (Grade 2B)	
Secondary prevention for symptomatic PAD	• Aspirin* 75–100 mg/day ***or*** clopidogrel 75 mg/day (Grade 1A) • Do not use antiplatelet therapy with moderate-intensity warfarin (Grade 1B)	Do not use dual antiplatelet therapy with aspirin plus clopidogrel (Grade 2B)
Intermittent claudication refractory to exercise therapy (and smoking cessation)		• Cilostazol* plus aspirin 75–100 mg/day or clopidogrel 75 mg/day (Grade 2C) • Avoid pentoxifylline, heparinoids, prostanoids (Grade 2C)
Symptomatic PAD with critical leg ischemia/rest pain, not candidates for vascular intervention		Prostanoids plus aspirin* 75–100 mg/day or clopidogrel 75 mg/day (Grade 2C)
Acute limb ischemia due to arterial emboli or thrombosis		Immediate systemic anticoagulation with UFH* (Grade 2C) Recombinant tissue-type plasminogen activator (rt-PA) or urokinase in patients undergoing intra-arterial thrombolysis (Grade 2C)
Percutaneous transluminal angioplasty		
Peripheral-artery PTA (with or without stenting)	Long-term aspirin* 75–100 mg/day ***or*** clopidogrel* 75 mg/day (Grade 1A)	For patients undergoing peripheral artery PTA with stenting, single rather than dual antiplatelet therapy (Grade 2C)
Vascular reconstruction		
Peripheral-artery bypass graft surgery	• Aspirin* 75–100 mg/day ***or*** clopidogrel* 75 mg/day (Grade 1A) • Single antiplatelet therapy recommended over antiplatelet therapy plus warfarin (Grade 1B)	
Below-knee bypass graft surgery with prosthetic grafts		Clopidogrel* 75 mg/day plus aspirin* 75–100 mg/day suggested over aspirin alone for 1 y (Grade 2C)
All other patients		Single rather than dual antiplatelet therapy (Grade 2C)
Carotid endarterectomy		
Asymptomatic carotid stenosis		Aspirin* 75–100 mg/day (Grade 2B)
Symptomatic carotid stenosis (including recent carotid endarterectomy)	Long-term antiplatelet therapy with clopidogrel* 75 mg/day, ASA/ERD* 25 mg/200mg/day, ***or*** aspirin* 75–100 mg/day (Grade 1A)	Clopidogrel 75 mg/day ***or*** ASA/ERD 25 mg/200mg/day suggested over aspirin 75–100 mg/day (Grade 2B)

PAD: peripheral artery disease; PTA: percutaneous transluminal angioplasty; UFH: unfractionated heparin.

Adapted from Alonso-Coello et al, 2012[3]

Valvular and Structural Heart Disease

Current ACCP recommendations for the management of valvular heart disease are summarized in Table 5.3.

TABLE 5.3. ACCP Recommendations for the Management of Valvular and Structural Heart Disease

Note: * denotes agents with an FDA-approved indication for the recommended use. (Antiplatelet agents are generally indicated for thromboprophlaxis.)

Patient Category	Recommendations	Suggestions
Rheumatic mitral valve disease		
NSR with left atrial diameter less than 55 mm		No antiplatelet or VKA therapy (Grade 2C)
NSR with left atrial diameter greater than 55 mm		VKA therapy (INR, 2.5; range, 2.0–3.0) over no VKA or antiplatelet therapy (Grade 2C)
With left atrial thrombus	VKA therapy (target INR, 2.5; range, 2.0–3.0) over no VKA therapy (Grade 1A)	
With AF or previous systemic embolism	VKA therapy (target INR, 2.5; range, 2.0–3.0) over no VKA therapy (Grade 1A)	
Being considered for PMBV		
Pre-procedural TEE shows left atrial thrombus	• Postpone PMBV • Administer VKA therapy (target INR, 3.0; range, 2.5–3.5) until thrombus resolution is documented by repeat TEE over no VKA therapy (Grade 1A)	
Left atrial thrombus does not resolve with VKA therapy	• Do not perform PMBV (Grade 1A)	
Patent foramen ovale or atrial septal aneurysm		
Asymptomatic		No antithrombotic therapy (Grade 2C)
Cryptogenic stroke	Aspirin* (50–100 mg/day) over no aspirin (Grade 1A)	
Recurrent events despite aspirin therapy		VKA therapy (target INR, 2.5; range, 2.0–3.0) and consider device closure over aspirin therapy (Grade 2C)
Cryptogenic stroke and PFO, with evidence of DVT	VKA therapy for 3 mo (target INR, 2.5; range, 2.0–3.0) (Grade 1B)	Consider device closure over no VKA therapy or aspirin therapy (Grade 2C)
Endocarditis		
Infective endocarditis	No routine antiplatelet therapy (Grade 1B) or anticoagulant therapy (Grade 1C), unless a separate indication exists	
Develops IE while on VKA for prosthetic valve		Discontinue VKA at initial presentation until it is clear that invasive procedures will not be required and patient has stabilized without signs of CNS involvement. When deemed stable without contraindications or neurologic complications, restart VKA therapy (Grade 2C)

TABLE 5.3 Continued
ACCP Recommendations for the Management of Valvular and Structural Heart Disease
Note: * denotes agents with an FDA-approved indication for the recommended use. (Antiplatelet agents are generally indicated for thromboprophlaxis.)

Patient Category	Recommendations	Suggestions
Aortic bioprosthetic valves		
In sinus rhythm, no other indication for VKA therapy		Aspirin (50–100 mg/day) over VKA therapy in first 3 mo (Grade 2C)
Transcatheter aortic bioprosthetic valves		Aspirin (50–100 mg/day) plus clopidogrel (75 mg/day) over VKA therapy and over no antiplatelet therapy in first 3 mo (Grade 2C)
Valve in mitral position		VKA therapy (target INR, 2.5; range, 2.0–3.0) over no VKA therapy for first 3 mo after valve insertion (Grade 2C)
NSR		Aspirin therapy over no aspirin therapy after 3 mo postoperative (Grade 2C)
Mechanical heart valves		
	VKA therapy (warfarin*) over no VKA therapy for long-term management (Grade 1B)	Bridging with UFH* (prophylactic dose) or LMWH (prophylactic or therapeutic dose) over IV therapeutic UFH until stable on VKA therapy (Grade 2C)
Mechanical aortic valve	VKA therapy (warfarin*) (target INR 2.5; range 2.0–3.0 over higher targets) (Grade 1B)	VKA therapy (target INR 2.5; range, 2.0–3.0 over lower targets) (Grade 2C)
Mechanical mitral valve		VKA therapy (target INR 3.0; range, 2.5–3.5 over lower INR targets) (Grade 2C)
Mechanical heart valves in both aortic and mitral positions		Target INR 3.0 (range 2.5–3.5) over target INR 2.5 (range 2.0–3.0) (Grade 2C)
Mechanical aortic or mitral valves	VKA therapy (warfarin*) over antiplatelet agents (Grade 1B)	
Mechanical mitral or aortic valve, low risk of bleeding	Add antiplatelet agent (e.g., aspirin 50–100 mg/day) to VKA therapy (Grade 1B) **Note:** Use caution in patients at increased bleeding risk (e.g., history of GI bleeding)	
Mitral valve repair with prosthetic band, in NSR		Antiplatelet therapy for first 3 mo over VKA therapy (Grade 2C)
Aortic valve repair		Aspirin 50–100 mg/day over VKA therapy (Grade 2C)
Right-sided PVT		In absence of contraindications, administer fibrinolytic therapy over surgical intervention (Grade 2C)
Left-sided PVT, large thrombus area (greater than 0.8 cm)		• Early surgery over fibrinolytic therapy (Grade 2C) • If contraindications to surgery exist, use fibrinolytic therapy (Grade 2C)

TABLE 5.3 Continued
ACCP Recommendations for the Management of Valvular and Structural Heart Disease
Note: * denotes agents with an FDA-approved indication for the recommended use. (Antiplatelet agents are generally indicated for thromboprophlaxis.)

Patient Category	Recommendations	Suggestions
Left-sided PVT, small thrombus area (less than 0.8 cm)		• Fibrinolytic therapy over surgery • For very small, nonobstructive thrombus, IV UFH accompanied by serial Doppler echocardiography to document thrombus resolution or improvement over other alternatives (Grade 2C)

AF: atrial fibrillation; CNS: central nervous system; DVT: deep venous thrombosis; GI: gastrointestinal; IE: infective endocarditis; INR: international normalized ratio; IV: intravenous; LMWH: low-molecular-weight heparin; NSR: normal sinus rhythm; PFO: patent foramen ovale; PMBV: percutaneous mitral balloon valvuloplasty; PVT: prosthetic valve thrombosis; TEE: transesophageal echocardiography; UFH: unfractionated heparin; VKA: vitamin K antagonist.

Adapted from: Whitlock et al, 2012[4]

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6. MANAGING THE RISKS OF MAJOR BLEEDING EVENTS ASSOCIATED WITH ANTITHROMBOTIC THERAPY

Antithrombotic therapy can reduce cardiovascular death, heart attack, stroke, and venous thrombosis, but this benefit is accompanied by an increased risk of bleeding that may range from a nuisance to a life-threatening event. This section discusses the bleeding risks associated with antithrombotic therapy and some strategies for reducing these risks.

Risk of Bleeding With Antithrombotic Therapy

A 2008 review of clinical studies of patients with various indications for warfarin in which anticoagulant intensity was carefully monitored concluded that treatment with VKA increased the risk of major bleeding by 0.3% to 0.5% per year and the risk of intracranial hemorrhage (ICH) by approximately 0.2% per year compared with that in untreated controls.[1] In ACCP 2012, VKA therapy was calculated to increase the risk of nonfatal major extracranial bleeding in patients with atrial fibrillation by 0.8% per year.[2] The differences in these risk estimates reflect the different approaches used by the authors to combine, compare, and contrast bleeding rates among those using and not using VKA therapy.

It may not be appropriate to extrapolate rates of adverse events from randomized controlled trials to everyday practice because high-risk patients may be excluded from clinical trials and the monitoring and management of anticoagulation are often better coordinated in clinical trials than in clinical practice. In routine clinical practice, the risk of major bleeding during prolonged anticoagulant therapy has been reported to be higher: between 1.7% and 3.4% per year.[1]

Information on rates of bleeding from different combinations of aspirin, clopidogrel, and VKA comes almost entirely from observational studies. The best available data are from a cohort study assessing the risk of bleeding in 118,606 Danish patients with atrial fibrillation (AF) who were treated with different combinations of aspirin, clopidogrel, and warfarin.[3] In this study, bleeding was defined as an admission to a Danish hospital, excluding emergency department visits, with a bleeding diagnosis or a diagnosis of bleeding as the cause of death. For patients taking aspirin and warfarin, the risk of bleeding was almost twice as high as that for patients receiving warfarin monotherapy. Patients receiving dual therapy with warfarin and clopidogrel and patients receiving triple oral antithrombotic therapy had the highest risk of bleeding.[3] Consequently, combination therapy should be carefully considered and given only for a short time when treatments are mandatory.

Bleeding risk should be assessed before antithrombotic medications are initiated. The two most common bleeding-risk models are the HEMORR2HAGES risk index[4] and the HAS-BLED risk score.[5] Another bleeding-risk tool is the RIETE Registry bleeding score.[6]

The HEMORR2HAGES risk index consists of 11 risk factors for bleeding: hepatic or renal disease, ethanol abuse, malignancy, age over 75 years, reduced platelet count or function (including aspirin therapy), rebleeding risk (history of prior bleed), hypertension, anemia, genetic factors, excessive fall risk, and stroke. Each factor is given one point except for rebleeding risk, which is given 2 points.[4]

The HAS-BLED risk score consists of seven items: hypertension, abnormal renal or liver function, stroke, bleeding history or predisposition, labile INR, elderly age

(over 65 years), and concomitant drug or alcohol use. It is performed similarly to the HEMORR2HAGES index and is simpler to apply.[5]

The RIETE Registry bleeding score includes six items: recent major bleeding, creatinine greater than 1.2 mg/dl, anemia, cancer, clinically overt pulmonary embolism, and age over 75 years. The scores for each item range from 1 to 2 points (Table 6.1).[6]

TABLE 6.1. Rates of Bleeding With Different Antithrombotic Single-Agent and Combination-Therapy Regimen

Treatment Regimen	Incidence Rate (% per patient year)		
	Bleeding	ICH	GI Bleeding
Aspirin alone	3.7	0.5	1.5
Warfarin alone	3.9	0.6	0.9
Clopidogrel alone	5.6	1.0	1.9
Warfarin plus aspirin	6.8	0.8	2.1
Dual antiplatelet therapy			
Clopidogrel plus aspirin	7.4	0.2	3.1
Warfarin plus clopidogrel	13.9	0.8	3.8
Triple oral antithrombotic therapy (warfarin plus aspirin plus clopidogrel)	15.7	1.0	5.1

GI: gastrointestinal; ICH: intracranial hemorrhage.

Source: Hansen et al, 2010[3]

The risk of GI bleeding with aspirin is dose dependent. Thus, aspirin doses of 75 mg/day are associated with a 30% lower risk of GI bleeding than are doses of 150 mg/day and a 40% lower risk than are doses of 300 mg/day.[7] The risk of upper GI bleeding associated with low-dose aspirin is comparable to the risk with other antiplatelet and anticoagulant drugs.[7]

The risk of aspirin-related bleeding is not reduced by substituting an enteric-coated or buffered formulation of aspirin.[7] The rate of bleeding caused by aspirin therapy is further increased among patients with risk factors such as older age, chronic kidney disease, diabetes, female gender, and a history of hypertension.[8]

As is the case with aspirin, bleeding risk with dabigatran is dose dependent. In the RE-LY study of patients with AF, the annual incidence of major bleeding was 3.4% in patients taking warfarin, 3.1% with dabigatran 150 mg bid, and 2.7% with dabigatran 110 mg bid.[9] Both dabigatran regimens reduced the likelihood of intracranial bleeding by more than 50% compared with warfarin; the annual incidence was 0.74% with warfarin, 0.30% with dabigatran 150 mg, and 0.23% with dabigatran 110 mg.

Reported rates of any bleeding with rivaroxaban in four phase III clinical trials in patients undergoing total hip or total knee replacement surgery range from 4.9% to 10.5% and are comparable to the rates observed in patients treated with enoxaparin.[10] Rates of major bleeding events range from 0.1% to 0.7%, whereas rates of clinically relevant nonmajor bleeding events range from 2.6% to 3.3%, again with no statistically significant differences between the rates observed in the rivaroxaban groups versus the comparator groups (the low-molecular-weight heparin enoxaparin in all studies).

In December 2011 the U.S. Food and Drug Administration (FDA) issued a safety alert concerning postmarketing reports of serious bleeding events with dabigatran.[11]

The median age of those with reported events was 80 years. No antidote exists to reverse bleeding with dabigatran or rivaroxaban. An American Geriatrics Society expert panel recommended in February 2012 that dabigatran be used with caution in adults aged 75 and older, but noted that bleeding risk may be offset in the highest-risk older adults.[12]

Anticoagulation intensity is the most important factor influencing bleeding risk. The likelihood of bleeding rises steeply with an international normalized ratio (INR) above 5.0. Patient-specific factors also increase the risk of bleeding during anticoagulant therapy. These patient-specific factors include the following[6,10,13]:

- Advanced age (specifically, age over 75 years),
- Alcohol abuse,
- Anemia,
- Cancer,
- Chronic hepatic disease,
- Clinically overt pulmonary embolism,
- Concomitant use of antiplatelet drugs,
- Hypertension,
- Poor INR monitoring and control,
- Prior stroke,
- Prior gastrointestinal bleeding in the absence of a reversible cause (e.g., use of nonsteroidal anti-inflammatory agents),
- Recent major bleeding, and
- Renal impairment.

ICH is the most serious and lethal complication of antithrombotic therapy, causing 90% of the deaths and most of the disability from warfarin-associated bleeding.[14] In patients treated with warfarin, the risk of ICH increases with advancing age and anticoagulation intensity. Specifically, as shown in a case-control study, the risk for ICH increases at age 85 and at an INR above 3.5.[15] Hypertension also increases the risk of ICH.

Reducing the Risk of Bleeding With Antithrombotic Therapy

To reduce the risk of bleeding with antithrombotic therapy, it is prudent to use the lowest doses of aspirin (below 100 mg/day).[7] In addition, when using VKA, the INR should be maintained in the lowest range, usually between 2.0 and 3.0.[10] Administration of a proton pump inhibitor (PPI) and eradication of *Helicobacter pylori* (*H. pylori*; see below) are also effective in reducing the risk of GI bleeding.[7] PPI use is associated with some adverse effects. These are discussed in detail below. In addition, blood pressure control (below 140/90) will help to reduce the risk of ICH.[16]

Role of Helicobacter pylori *in Bleeding Risk*

In addition to using the lowest effective dose of aspirin and prophylactically prescribing a PPI or other gastroprotective agent, another strategy to decrease the risk of GI bleeding from antiplatelet therapy is to screen for and treat *H. pylori* infection if present.[17,18] The benefit of *H. pylori* eradication is more marked in those people who are beginning therapy with antithrombotics than in those already tolerating antithrombotic therapy.[19]

An expert panel from the American Heart Association and American College of Gastroenterology has recommended screening for and eradicating *H. pylori* infection

before beginning chronic antiplatelet therapy.[18] The panel recommended using either the fecal antigen or urea breath test, but not serological tests, to diagnose active *H. pylori* infection.[18] The panel recommended against using serum antibody testing to diagnose active *H. pylori* infection because antibodies remain positive even after eradication.

In the long term care (LTC) setting, routinely screening for and eradicating *H. pylori* infection before beginning antiplatelet therapy may be impractical. The diagnostic workup for a patient with an acute GI bleed, however, should include testing for *H. pylori* infection. In the setting of upper GI bleeding, the fecal antigen test and urea breath test have high positive predictive value (0.85 and 0.97, respectively) and modest negative predictive value (0.75 and 0.73 respectively).[20] Therefore, if an initial test result is negative, the test should be repeated. False negative results from the urea breath test may be observed in patients who are taking PPIs, bismuth, or antibiotics.

Potential Adverse Effects of Proton Pump Inhibitors (PPI)

Studies have suggested an association between PPI use and an increased risk for pneumonia and *Clostridium difficile* (*C. diff.*) infection. One meta-analysis of eight observational studies found that patients taking PPIs or H_2-receptor antagonists had an increased risk of pneumonia.[21] A significant dose response was observed in PPI users who took more than one dose per day; these users had a 2.3-fold increased risk of pneumonia compared with past users of acid-suppressive agents. This dose response was not observed with H_2-receptor antagonists.[22] A meta-analysis of 30 observational studies involving more than 200,000 patients found that PPI use was significantly associated with increased risk of *C. diff.* infection.[23]

PPI use may also be associated with malabsorption of vitamin B_{12}, magnesium, and calcium, resulting in B_{12} deficiency, hypomagnesemia, and hip fracture. In March 2011, the FDA issued a safety alert to health care professionals and consumers concerning the potential for PPIs to cause hypomagnesemia if taken for more than 1 year.[24] The FDA recommended that health care professionals consider obtaining serum magnesium levels before initiating PPI treatment and periodically in patients expected to be taking these drugs long term.

A case-control study suggested that long term use of PPIs was associated with a slightly increased risk of hip fractures in patients aged over 50 and that the magnitude of the increased risk was proportional to both the PPI dose and the duration of therapy.[25] A meta-analysis of 11 cohort and case-control studies also examined the risk of fractures associated with PPI use in more than 1 million patients[26]; the risk of hip fracture was increased among PPI users compared with nonusers. PPI users, compared with nonusers, also had an increased risk of spine fracture and any-site fracture. The risk is greatest when prescription PPIs are taken for at least 1 year. In May 2010, the FDA revised the safety information on prescription PPIs to reflect this increased fracture risk. In March 2011, however, the FDA determined that the same warning was not indicated on the over-the-counter PPI, which is marketed at lower doses and for shorter durations (a 14-day course to be repeated up to three times in a year).[27]

In the LTC setting, in which PPIs are frequently prescribed at low doses for long term use, the practitioner may conclude that, for patients using antiplatelet agents, the benefits of long term acid-suppressive therapy to reduce GI bleeding risk may

outweigh the risks. Patients on long-term PPI therapy should be reassessed periodically to determine whether the benefits continue to outweigh the risks. When discontinuing PPI therapy, doses usually should be tapered slowly and the patient should be monitored for symptoms of acid secretion (e.g., abdominal discomfort, change in appetite, heartburn).

Among the PPIs, omeprazole and lansoprazole, which are metabolized largely via CYP2C19, seem to present the greatest risk for drug-drug interactions. Pantoprazole and rabeprazole are less likely to be involved in drug-drug interactions.[28] Misoprostol is an alternative to a PPI for providing gastric cytoprotection, but for many patients the side effect of diarrhea limits its acceptability.[18]

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7. ANTIPLATELET AGENTS IN ANTITHROMBOTIC THERAPY

Aspirin

The optimal dose of aspirin for different indications is variable. In general, to limit adverse effects, it is prudent to use the lowest effective dose.

ACCP 2012 recommends

- Aspirin 75 mg/day to 100 mg/day for primary prevention of cardiovascular disease in patients aged 50 or older (Grade 2B),[1]
- Aspirin 75 mg/day to 100 mg/day for primary prevention of cardiovascular events in patients with asymptomatic peripheral artery disease (PAD) (Grade 2B),[2] and
- Aspirin 75 mg/day to 100 mg/day or clopidogrel 75 mg/day for secondary prevention of cardiovascular disease in patients with symptomatic PAD (Grade 1A).[2]

ACCP 2012 suggests ***against*** dual therapy with aspirin plus clopidogrel (Grade 2B) and ***against*** using antiplatelet therapy with warfarin (Grade 1B) for secondary prevention of cardiovascular events in patients with symptomatic PAD.[1]

In patients with atrial fibrillation (AF) at low risk of stroke (CHADS score 0; see Table 4.5) who request antithrombotic therapy, ACCP 2012 suggests aspirin 75 mg/day to 325 mg/day (Grade 2B).[3]

In patients with established coronary artery disease (CAD) who are 1 year post acute coronary syndrome with revascularization and have coronary stenosis of greater than 50% or evidence of cardiac ischemia, ACCP 2012 recommends long term single antiplatelet therapy with aspirin 75 mg/day to 100 mg/day or clopidogrel 75 mg/day (Grade 1A). Single antiplatelet therapy is preferred over dual antiplatelet therapy with aspirin plus clopidogrel (Grade 2B). For patients who are less than 1 year post acute coronary syndrome, antithrombotic therapy will depend on stent type.[1]

Caution is advised in prescribing aspirin to patients with a history of gastroesophageal reflux disease (GERD), gastrointestinal (GI) bleeding, peptic ulcer disease, thrombocytopenia, or uncontrolled hypertension. Aspirin is contraindicated in patients who have asthma, gout, hemorrhagic disorders, or urticaria induced by aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs), or a history of intolerance to aspirin therapy. Aspirin should be avoided in patients with severe renal failure (defined in the product labeling as glomerular filtration rate below 10 ml/min).[4]

A meta-analysis of randomized trials of antiplatelet therapy evaluated the effects of antiplatelet therapy among patients at high risk for occlusive vascular events.[5] This analysis included 287 trials, involving more than 200,000 patients, in which aspirin was compared with a control therapy. The full antiplatelet effect of aspirin was seen at doses of 75 mg/day to 80 mg/day; there is no evidence that higher doses are more effective in preventing secondary events.

Clopidogrel (Plavix)

Clopidogrel 75 mg/day is indicated for[6]

- Acute coronary syndrome,
- ST-segment elevation myocardial infarction (STEMI),
- Non-ST-segment elevation myocardial infarction (NSTEMI),

- Recent myocardial infarction,
- Recent stroke, or
- Established peripheral artery disease.

Clopidogrel has been shown to reduce the rate of a combined endpoint of new ischemic stroke (fatal or not), new MI (fatal or not), and other vascular death for these indications.[6]

Clopidogrel is contraindicated in patients with active bleeding and in those demonstrating hypersensitivity to the drug or any of it components. Clopidogrel requires no dose adjustment in the geriatric population and no hematologic monitoring.

Coadministration of clopidogrel and NSAIDs increases the risk of GI bleeding. Coadministration of clopidogrel and warfarin increases the risk of bleeding because of the combined effect of these two medications on hemostasis.

Thrombotic thrombocytopenic purpura, a potentially fatal condition, has been reported with the use of clopidogrel, sometimes after a short exposure (less than 2 weeks).

In March 2010 the U.S. Food and Drug Administration (FDA) added a boxed warning to clopidogrel's labeling concerning patients who do not effectively metabolize the drug because of the presence of an altered form of the gene for the liver enzyme CYP2C19. Patients who are poor metabolizers as a result of low CYP2C19 activity do not effectively convert clopidogrel (a prodrug) to its active form; usual doses will therefore have a diminished effect on platelet function in these patients. Although a higher-dose regimen increases the antiplatelet response in poor metabolizers, an appropriate dose regimen has not been established for these patients.[7,8]

Tests are available to identify a patient's CYP2C19 genotype; however, these tests are typically not performed in the LTC setting and the information is rarely available in transfer records for patients who are newly admitted or readmitted to LTC facilities. Genetic testing for CYP2C19 metabolism status is not recommended in the LTC setting. If a patient being treated with clopidogrel in the LTC setting is hospitalized after experiencing a cardiovascular event, however, the practitioner should consider asking whether the patient's CYP2C19 genotype status was tested while he or she was hospitalized and, if so, requesting the test result.

With regard to the potential for an adverse interaction between proton pump inhibitors (PPIs) and clopidogrel, resulting in a reduction in the antiplatelet effectiveness of clopidogrel, the current evidence is reassuring.[9,10] In the only large-scale randomized trial of the PPI omeprazole versus placebo in clopidogrel users, there was no significant difference in cardiovascular events when clopidogrel was combined with omeprazole, but there was a significant reduction in GI bleeding.[9]

Extended-Release Dipyridamole/Aspirin (ERD/ASA; Aggrenox)

ERD/ASA 25/200 mg/day is indicated to reduce the risk of stroke in patients who have had a thrombosis-related TIA or stroke.[11]

Caution is advised in prescribing ERD/ASA if the patient has a coagulation disorder, thrombocytopenia, an intracranial lesion or increased intracranial pressure, a history of GI bleeding, GERD, coronary artery disease, hypotension, significant renal or hepatic impairment, or current significant alcohol intake. Caution is also advised if the patient is to have surgery or if any episode of significant trauma occurs during treatment.

ERD/ASA is contraindicated in patients who are hypersensitive to either dipyridamole or aspirin or who have aspirin- or NSAID-induced asthma or urticaria. Additional contraindications commonly seen in the LTC setting include G6PD deficiency, active peptic ulcer disease, GI bleeding, and uncontrolled hypertension. ERD/ASA should be avoided in patients with severe hepatic impairment. It appears that no dosage adjustment of ERD/ASA is needed in patients with mild to moderate hepatic insufficiency. Aspirin and any medication combined with aspirin should be avoided in patients with severe renal failure (defined in the product labeling as glomerular filtration rate below 10 ml/min).

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8. WARFARIN IN ANTITHROMBOTIC THERAPY

Warfarin (Coumadin®) is the most commonly used anticoagulant in the LTC setting. Warfarin is indicated to

- Prevent or treat venous thrombosis and its extension, pulmonary embolism;
- Prevent or treat thromboembolic complications associated with atrial fibrillation (AF) or cardiac valve replacement; and
- Reduce the risk of death, recurrent myocardial infarction (MI), and thromboembolic events such as stroke or systemic embolization after MI.

Warfarin is contraindicated in patients with the following medical conditions:

- Any localized or general physical condition or personal circumstance in which the hazard of hemorrhage might be greater than the potential clinical benefits of anticoagulation;
- Bleeding tendencies associated with active ulceration or overt bleeding of the gastrointestinal, genitourinary, or respiratory tract or the cerebrovascular system;
- Evidence of bacterial endocarditis, cerebral aneurysm, dissecting aorta, pericarditis, or pericardial effusions;
- Hemorrhagic tendencies or blood dyscrasia;
- Large postoperative wounds; or
- Recent surgery of the central nervous system or eye.

Assessment for Warfarin Use in Antithrombotic Therapy

Before initiating warfarin, practitioners must consider several factors: indication(s) for therapy, contraindications to anticoagulation, comorbid conditions and medication interactions that influence warfarin metabolism, bleeding risk, and patient prognosis and preferences.

First, assess whether anticoagulation might improve the quality or length of the patient's life. If the patient has advanced disease and a poor prognosis, warfarin may not provide a meaningful benefit. (See Appendix 4 for a worksheet that can assist the practitioner in assessing the risks and benefits of warfarin use.)

Next, assess whether the patient has any absolute contraindications to warfarin use. Absolute contraindications to warfarin include bleeding diathesis, noncompliance with medications or monitoring, platelet count below 50,000, and uncontrolled hypertension (over 160/90 mm Hg).[1] Relative contraindications include alcohol intake of more than 2 oz daily and regular use of a nonselective nonsteroidal anti-inflammatory drug (NSAID) without cytoprotection. Warfarin may be used cautiously if patients also are prescribed either a cyclo-oxygenase 2–specific (COX-2) NSAID or a nonselective NSAID plus misoprostol or a proton pump inhibitor (PPI); however, a COX-2 NSAID still increases the risk of gastrointestinal (GI) bleeding 1.7- to 2.4-fold.[2] Warfarin can be used once peptic ulcer bleeding has resolved and following *Helicobacter pylori* testing and treatment.[1,3] (Please also see Chapter 6, **Managing the Risks of Major Bleeding Events Associated with Antithrombotic Therapy**.)

In the elderly population the risk of falling should not be an absolute or relative contraindication to warfarin therapy.[4] The increased risk for stroke manifested by a CHADS-2 score of 2 or higher (see Table 4.5) outweighs the risk of intracranial hemorrhage in patients who are at risk for falls and would benefit overall from anticoagulation. It has been calculated that a patient taking warfarin must fall almost 300

times in 1 year for the fall risk to outweigh the benefit obtained from the vitamin K antagonist (VKA).[5]

Comorbid Conditions and Medication Interactions

Next, the practitioner should review the patient's medications and medical conditions to seek opportunities to reduce the risk of bleeding. The potential for warfarin to increase intracerebral and subdural bleeding causes the greatest degree of concern among both practitioners and patients. These serious, potentially fatal complications may negatively affect decisions about prescribing warfarin. Documentation of a decision to use warfarin should include a plan to reduce bleeding risks. (See Chapter 6, **Managing the Risks of Major Bleeding Events Associated with Antithrombotic Therapy**.)

Some evidence suggests that the risks of bleeding while taking warfarin may be reduced by controlling blood pressure, limiting alcohol consumption, prescribing a gastric cytoprotectant (i.e., a PPI or misoprostol) if patients are taking aspirin or an NSAID, and treating *H. pylori* infection.[1] Because hypertension increases the risk of intracranial hemorrhage, control of blood pressure (below 140/90) should be achieved when a patient is receiving warfarin, and warfarin should not be initiated in a patient with uncontrolled hypertension.[6,7] A comprehensive evaluation for fall risk factors, with appropriate interventions, may reduce the occurrence of falls.

Note that in up to 30% of patients, the GI or genitourinary bleeding that occurs during warfarin therapy may be due to occult malignancy.[2,5] When bleeding occurs during warfarin therapy, the practitioner should inform the patient or family about the risk of occult malignancy and decide whether the benefits of a diagnostic evaluation outweigh its associated burdens.

In addition to assessing bleeding risk, stroke risk should be assessed for patients with atrial fibrillation (AF) using the CHADS-2 score (see Table 4.5). The benefits of VKA therapy generally outweigh the risk when the CHADS-2 score is 1 or higher.[8]

Shared Decision Making About Warfarin Use

Practitioners often are hesitant to prescribe warfarin to patients of increasing age and frailty. A cross-sectional analysis of prescription and patient data from the 2004 National Nursing Home Survey found that among 1,767 patients residing in LTC facilities who had AF and no contraindications to warfarin, warfarin was prescribed in only 30% of cases; in 54% of patients, no antithrombotic therapy was prescribed.[9]

When patients are included in risk-benefit discussions about warfarin use, they may reach a decision that differs from that of the practitioner. For this reason, it is prudent to inform patients about the benefits and burdens of warfarin therapy and reach a shared decision about warfarin use. A systematic review of 48 studies that examined patient preferences for antithrombotic therapy found that, overall, patients tended to place a higher disutility value on stroke than on GI bleeding and a much higher disutility value on stroke than on treatment burden. (Disutility value refers to the burden or negative outcomes associated with a particular health state.)[10]

Prescribing of Warfarin for Antithrombotic Therapy

Warfarin should be prescribed on the first day of venous thromboembolism (VTE) treatment, the same day parenteral therapy is started (Grade 1A). Warfarin's antithrombotic effect requires depletion of prothrombin (factor II), which may take from

6 days to as long as a few weeks, depending on the warfarin dose and clinical factors. For this reason, patients with an acute VTE must receive concomitant unfractionated heparin (UFH), low-molecular-weight heparin, or fondaparinux for at least 5 days, regardless of the international normalized ratio (INR) value. After the initial 5 days of overlapping treatment, the parenteral anticoagulant may be stopped when the INR measurement is at least 2.0 (Grade 1A).[11]

Target INR During Warfarin Therapy

For patients treated with warfarin for VTE, a therapeutic INR range of 2.0 to 3.0, with a target of 2.5, is recommended. For patients with antiphospholipid syndrome with previous thromboembolism, the INR range is titrated to a range of 2.0 to 3.0 rather than to a higher intensity.

The INR may fluctuate during the first weeks of warfarin therapy. During this time, in patients who have more than one subtherapeutic INR, practitioners should consider resuming the parenteral anticoagulant until warfarin dose adjustments produce a therapeutic INR (a subtherapeutic INR increases the risk of VTE recurrence). No established practice guidelines exist, however, regarding the INR level that warrants bridging therapy with parenteral anticoagulation.[12] Two studies suggest consideration of action for an INR between 1.7 and 1.5. One study showed a tripling of the risk of recurrent deep vein thrombosis when the INR is below 1.5[13]; another showed a doubling of stroke risk from AF when the INR drops to 1.7.[14] A third study noted a similar increased risk but emphasized that the relatively low absolute increase (0.6%) in acute VTE when the INR was at or below 1.5 may argue against bridging during dose adjustment to raise the INR.[15]

Initiation Doses of Warfarin

Clinical studies suggest that initiation doses of warfarin between 5 and 10 mg are effective; individual responses vary by inpatient or outpatient status, age, concurrent treatments, and comorbidities.

The 9th edition of the American College of Chest Physicians evidence-based guidelines on antithrombotic therapy and thrombosis (ACCP 2012) suggests against thromboprophylaxis with any antithrombotic agent for chronically immobilized patients at home or in an LTC facility (Grade 2C). In patients who are "sufficiently healthy to be treated as outpatients," ACCP 2012 suggests initiating warfarin at a dose of 10 mg/day for 2 days, followed by dosing based on INR measurements (Grade 2C).[16] This suggestion is based on a review of a case series of outpatients whose average age was 20 to 30 years younger than that of the average patient in the LTC setting. Although this initiation and dosing algorithm may be appropriate for a subset of relatively robust (usually short-stay) LTC patients, as well as for many patients in assisted living settings, a 10 mg starting dose may not be appropriate for frailer, older, more complex patients in this setting. Starting doses of 5 mg are suggested in older adults; patients with impaired nutrition, liver disease, or congestive heart failure; and patients at high risk for bleeding. An initial dose of 2 to 3 mg may be appropriate for patients who have undergone heart valve replacement and thus have a higher sensitivity to VKAs, most likely because of the effects of cardiopulmonary bypass and concurrent therapies[2]; subsequent dose adjustments should follow established algorithms.

Occasionally, practitioners concerned about the occurrence of bleeding events during long-term warfarin therapy will prescribe low-intensity warfarin therapy (i.e., INR 1.5 to 1.9). Low-intensity warfarin is superior to placebo and can produce a 75% total risk reduction when used to prevent VTE recurrence,[17] but this effect is significantly less than the more than 90% risk reduction achieved with conventional-intensity warfarin therapy (INR range 2.0 to 3.0).[18] The risk of major hemorrhage is similar with low-intensity and conventional-intensity warfarin therapy.[17]

Duration of Warfarin Therapy[16]

The recommended duration of warfarin therapy varies according to the clinical situation associated with the VTE. Patients are less likely to have a recurrent VTE if their initial event was related to a reversible risk factor (e.g., surgery, acute illness requiring hospitalization, limb immobilization). Recurrence is more likely if the VTE involved a proximal vein, if initial treatment was incomplete, if the VTE was a second episode, if residual thrombus is present in the proximal vein after treatment, and in the presence of antiphospholipid antibody.

Duration of anticoagulation is described as short (4 to 6 weeks), intermediate (3 to 6 months), or indefinite (lifelong). A review of trials that randomized patients with VTE to 3 months versus 6 or 12 months of treatment found that 6 or 12 months of therapy did not convincingly lower the risk of VTE of recurrence but increased major bleeding about 2.5-fold. The ACCP 2012 panel concluded that although anticoagulants effectively prevent recurrence while patients are receiving therapy, the risk of recurrence after discontinuation of therapy is similar whether patients have been treated for 3 months or longer.[19]

Monitoring Warfarin Therapy

The practitioner should create a plan to monitor for potential warfarin adverse effects and to maintain the INR in the therapeutic range. Monitoring for adverse effects may include periodic testing of urine and stool for occult bleeding and checking hemoglobin for blood loss. Warfarin therapy must be monitored by periodic determination of prothrombin time/international normalized ratio (PT/INR). Numerous factors (e.g., diet, medications, botanicals, genetic variations in the CYP2C9 and VKORC1 enzymes) may influence the patient's response to warfarin. Routine pharmacogenetic testing for guidance on warfarin dosing is not recommended (Grade 1B).[16]

Close monitoring to keep INR values within the range of 2.0 to 2.5 may reduce bleeding risk because most bleeding events are associated with INR values higher than 3.0. Frequent INR monitoring is especially important when initiating warfarin therapy because bleeding risk varies over time. The risk of major bleeding is 3% during the first month of therapy, decreases to 0.8% per month in the subsequent 11 months, and stabilizes at 0.3% per month thereafter.[5]

The American Geriatrics Society guidelines for the use of warfarin in older adults recommend monitoring INR daily until stable and suggest that this be followed by testing two or three times weekly for 1 to 2 weeks, weekly for 1 month, and monthly thereafter.[20]

The ACCP's updated recommendations for INR monitoring in patients receiving warfarin are summarized in Table 8.1.

TABLE 8.1. Recommended INR Monitoring in Patients Receiving Warfarin

Clinical Situation	Action (Grade of Recommendation)
Consistently stable INR for 3 mo without adjustment of warfarin dose	INR may be tested at intervals up to12 weeks (2B)
Patient with consistently stable INR presents with a single INR value 0.5 above or below therapeutic target	Continue current warfarin dose; check INR again within 1–2 weeks (2C)
INR in range 4.5–10, no evidence of bleeding	Do not routinely administer Vitamin K (2B)
INR greater than 10, no evidence of bleeding	Administer oral Vitamin K (2B)
Warfarin-associated major bleeding	Initiate rapid reversal with prothrombin complex concentrate rather than plasma (2C) plus the use of Vitamin K 5–10 mg by slow IV rather than using coagulation factors alone (2C)

INR: international normalized ratio; IV: intravenous.

It is generally good practice to monitor the patient's response to warfarin therapy with additional PT/INR determinations at the following times:

- Immediately before, during, and after treatment with certain antibiotics. When prescribing antibiotics via a telephone order, the practitioner should determine from the facility nurse whether the patient is receiving warfarin and adjust the dose of warfarin accordingly, and/or order an INR to be drawn in 3 days and at least weekly during therapy with interacting antibiotics;
- Immediately after readmission to the LTC facility following hospitalization; and
- Whenever other medications, including botanicals, are initiated, discontinued, or taken irregularly. Please refer to AMDA's *Multidisciplinary Medication Management Manual*[a] for warfarin safety, therapeutic goals, and formulary management of Vitamin K antagonists.

Facility staff members should contact the practitioner with the results of all INRs and in the following clinical situations:

- Signs or symptoms of hemorrhage or thromboembolism are observed;
- The prescribed duration of warfarin therapy has been completed;
- The patient has missed a warfarin dose; or
- The pharmacist has notified the facility of a drug interaction with warfarin that would affect bleeding time and place the patient at risk for bleeding or hemorrhage.

Concurrent use of anti-infective agents in patients receiving warfarin may increase the risk of bleeding; the severity of the potential interaction depends on which anti-infective agent is prescribed. Medical directors may wish to implement a facility policy that staff members may not remove an antibiotic from the facility's emergency medication supply without first confirming whether or not the patient for whom the antibiotic is intended is receiving warfarin and then obtaining the practitioner's direction or seeking the advice of a pharmacist.

[a] AMDA. *Multidisciplinary Medication Management Manual*. Ordering information available at http://www.amda.com/resources/print.cfm#MED.

Health care providers should use a systematic and coordinated approach to managing anticoagulant therapy. This could involve using an anticoagulation management service (inpatient, outpatient, or provided by the LTC pharmacy) or incorporating patient education, systematic INR testing, tracking, follow-up, and good patient communication of results.[16] For dosing decisions during maintenance therapy, ACCP 2012 suggests using a validated decision support tool (paper nomogram or computerized dosing program) (Grade 2C).[16]

Appendixes 5–10 offer sample policies, templates, and other guidance to assist the practitioner in managing warfarin use in the LTC setting.

Conversions Between Warfarin and Other Anticoagulants

Established protocols exist for conversion from UFH to warfarin. Warfarin is generally initiated while the patient is still on full-dose UFH therapy. Generally, both medications are administered for 4 to 5 days until a therapeutic INR (i.e., more than 2.0 on 2 consecutive days) is confirmed.[21]

Warfarin therapy can be converted to dabigatran by discontinuing warfarin and starting dabigatran when the INR falls below 2.0. When converting from dabigatran to warfarin, dabigatran should be discontinued and warfarin should begin as shown in Table 8.2, based on renal function.

TABLE 8.2. Schedule for Converting from Dabigatran to Warfarin, Based on Renal Function

CrCl	Warfarin Start Date
More than 50 ml/min	Start warfarin 3 days before discontinuation of dabigatran
31–50 ml/min	Start warfarin 2 days before discontinuation of dabigatran
15–30 ml/min	Start warfarin 1 day before discontinuation of dabigatran
Less than 15 ml/min	No recommendation*

CrCl: creatinine clearance.

* CrCl less than 15 ml/min was an exclusion criterion in clinical trials of dabigatran.

Adapted from: Guidelines for Management of Patients on Dabigatran (Pradax®)[22]

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9. OTHER ORAL ANTICOAGULANTS IN ANTITHROMBOTIC THERAPY

Dabigatran (Pradaxa)

The oral anticoagulant dabigatran was approved by the FDA in October 2010 with an indication for thromboembolism prophylaxis in patients with nonvalvular atrial fibrillation (AF). Dabigatran's mechanism of action involves direct inhibition of thrombin. It is administered at a dose of 150 mg twice daily for patients who have a creatinine clearance (CrCl) that exceeds 30 mg/mL. For patients with CrCl of 30 mL/min or less, the dose is adjusted to 75 mg twice daily.

Dabigatran's labeling was revised in November 2011 to recommend assessment of renal function before initiation of therapy and at least once a year in patients with CrCl below 50 mL/min or aged 75 or older. The revised labeling also notes that the P-glycoprotein (P-gp) inhibitor dronedarone and systemic ketoconazole may interact adversely with dabigatran in patients with renal impairment. Practitioners should consider reducing the dabigatran dose to 75 mg twice daily in patients with moderate renal impairment (CrCl 30 to 50 mL/min) who are also receiving either of these agents. Dabigatran use is not recommended in patients with severe renal impairment (CrCl less than 30 mL/min) who are receiving concomitant P-gp inhibitors. The labeling also advises avoiding coadministration of dabigatran with the P-gp inducer rifampin.[1]

Dabigatran is contraindicated in patients with active pathological bleeding and in those with a history of a serious hypersensitivity reaction to the drug, including an anaphylactic reaction or anaphylactic shock.

Dabigatran should be discontinued 1 to 2 days before invasive surgery (e.g., dental extraction) if the patient's CrCl is at least 50 mL/min, 3 to 5 days prior to surgery if CrCl is less than 50 mL/min, and more than 5 days before major surgery (e.g., abdominal surgery), spinal puncture, or placement of a spinal or epidural catheter or port. If surgery cannot be delayed, the patient will be at increased risk for bleeding. This risk should be weighed against the urgency of intervention. Bleeding risk can be assessed by the ecarin clotting time (ECT) test, which is a better marker of the anticoagulant activity of dabigatran than activated partial thromboplastin time (aPTT), prothrombin time and international normalized ratio (PT/INR), or thrombin time (TT). If ECT testing is not available, the aPTT test provides an approximation of dabigatran's anticoagulant activity.

Conversions Between Dabigatran and Other Anticoagulants

To convert from a parenteral anticoagulant to dabigatran, start dabigatran *either* 0 to 2 hours before the time that the next dose of the parenteral drug was to have been administered *or* at the time of discontinuation of a continuously administered parenteral drug (e.g., intravenous unfractionated heparin).

For patients currently taking dabigatran, wait 12 hours (if CrCl is at or above 30 mL/min) or 24 hours (if CrCl is less than 30 mL/min) after the last dose of dabigatran before initiating treatment with a parenteral anticoagulant. For conversions from dabigatran to warfarin, please see **Chapter 8** (**Conversions Between Warfarin and Other Anticoagulants** and **Table 8.2**).

Rivaroxaban (Xarelto)

Rivaroxaban, a once-daily oral anticoagulant that is a direct, selective, reversible inhibitor of factor Xa, was approved by the U.S. Food and Drug Administration in July 2011 for prevention of venous thromboembolic events in patients who have undergone elective total hip or knee replacement surgery and in November 2011 for stroke prophylaxis in patients with nonvalvular AF. The dose and duration of postoperative treatment is 10 mg/day orally for 10 days for knee replacement surgery and 35 days for hip replacement surgery. In nonvalvular AF, 20 mg/day of rivaroxaban should be taken with the evening meal.

Caution is advised and dose adjustments may be required for patients with renal impairment (Tables 9.1, 9.2). Rivaroxaban use should be avoided in patients with severe renal impairment (CrCl less than 30 mL/min) and discontinued in the event of acute renal failure. Rivaroxaban use should also be avoided in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment or any hepatic disease associated with coagulopathy.

The rivaroxaban labeling advises avoiding concomitant use of this drug with agents that are inducers of P-gp or the enzyme CYP3A4 (e.g., carbamazepine, phenytoin, rifampin, St. John's wort). In patients with compromised renal function (CrCl 15 to 50 mL/min) who are concurrently receiving inhibitors of P-gp and CYP3A4, the risks versus the benefits of rivaroxaban use should be carefully considered. Concurrent use of rivaroxaban with other anticoagulants should be avoided. In the ROCKET-AF trial, concomitant use of aspirin (almost exclusively at a dose of 100 mg or less) with rivaroxaban was identified as an independent risk factor for major bleeding.[2]

Rivaroxaban increases risk for bleeding and can cause serious or fatal bleeding at any site. Use this agent with caution in conditions that carry an increased risk of hemorrhage. Concomitant use of drugs that affect hemostasis will increase bleeding risk.

TABLE 9.1. Use of Rivaroxaban for DVT Prophylaxis with Renal Impairment

Renal Function	Action
Moderate impairment (CrCl 30–50 mL/min)	Continue treatment while observing closely for signs or symptoms of blood loss
Severe impairment (CrCl less than 30 mL/min)	Avoid use due to expected increase in rivaroxoban exposure
Acute renal failure	Discontinue use

CrCl: creatinine clearance; DVT: deep-vein thrombosis.

TABLE 9.2. Use of Rivaroxaban for Nonvalvular Atrial Fibrillation with Renal Impairment

Renal Function	Dose Adjustment
CrCl greater than 50 mL/min	No dose adjustment. Prescribe 20 mg/day orally with the evening meal
CrCl 15–50 mL/min	Reduce dose to 15 mg/day orally with the evening meal
CrCl less than 15 mL/min	Discontinue treatment or avoid use
Acute renal failure	Discontinue treatment or avoid use

CrCl: creatinine clearance.

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10. PARENTERAL ANTICOAGULANTS IN ANTITHROMBOTIC THERAPY

The parenteral anticoagulants available in the United States are fondaparinux (Arixtra), a synthetic selective factor Xa inhibitor, and the low-molecular-weight heparins (LMWHs) enoxaparin (Lovenox), dalteparin (Fragmin), and tinzaparin (Innohep). These agents are not interchangeable because each has unique effects on antithrombin III and inhibition of factor Xa. Although the indications approved by the U.S. Food and Drug Administration (FDA) for each agent vary, these medications have similar adverse effects and precautions. Dosing of these agents for FDA-approved indications are summarized in Table 10.1.

Fondaparinux (Arixtra)[1]

Fondaparinux is a synthetic pentasaccharide anticoagulant used for the treatment of deep vein thrombosis (DVT) or pulmonary embolism (PE) and for the prevention of DVT and PE in patients undergoing abdominal surgery, hip fracture surgery, or hip or knee replacement surgery.

Fondaparinux should be injected subcutaneously; it is not suitable for intramuscular administration.

The presence of active major bleeding (e.g., gastrointestinal bleeding or acute hemorrhagic stroke), bacterial endocarditis, or known hypersensitivity to fondaparinux are contraindications to the use of fondaparinux. Prophylactic therapy with fondaparinux is also contraindicated in patients with body weight less than 50 kg who are undergoing hip fracture surgery, hip or knee replacement surgery, or abdominal surgery.

The presence of thrombocytopenia is a contraindication to the use of fondaparinux. Thrombocytopenia has occurred with fondaparinux. The manufacturer suggests that if platelet counts fall below 100,000/mm^3, fondaparinux should be discontinued.

The presence of severe renal disease, severe renal impairment (creatinine clearance [CrCl] below 30 ml/min), or renal failure are contraindications to the use of fondaparinux. Adequate renal function is required as fondaparinux is excreted primarily as the unchanged drug. Accumulation of the active drug greatly increases the risk for a major bleed, which is defined in clinical studies as fatal bleeding, nonfatal bleeding in a critical organ, bleeding requiring reoperation, or overt bleeding. Fondaparinux should be used cautiously in patients with moderate renal function (CrCl 30 to 50 ml/min). All patients receiving fondaparinux should be regularly evaluated for adequate renal function and the drug should be discontinued if severe renal impairment or labile renal function occurs.

As with other antithrombotic agents, fondaparinux should be used with extreme caution in patients with an increased risk of hemorrhage. Patients should be monitored closely for a fall in hematocrit and/or a fall in blood pressure, hematuria, hematemesis, and other signs or symptoms of bleeding. Periodic complete blood counts, serum creatinine levels, and stool occult blood tests are recommended. Unlike coumarins or heparinoids, an antidote to bleeding with fondaparinux is not available.

Fondaparinux should be used cautiously in geriatric patients, particularly in those aged 75 or older. Renal clearance in this population is reduced by roughly 25% and accumulation of the unbound active drug may lead to serious adverse events, including major bleeding. The risk of major bleeding increases with age. Renal parameters should be assessed before the use of fondaparinux in elderly patients.

Low-Molecular-Weight Heparins

Enoxaparin (Lovenox)

Enoxaparin is frequently included in the medication regimens of patients who are newly admitted or readmitted to long term care (LTC) facilities. This agent is indicated for

- DVT prophylaxis in inpatients who have had orthopedic surgery of the hip or knee; high-risk abdominal, gynecologic, or urologic surgery; or colorectal surgery;
- DVT prophylaxis in medical patients who are at moderate risk of DVT and are bedridden as a result of moderate to severe cardiac insufficiency (NYHA Class III or IV heart failure), acute respiratory failure that reveals or complicates chronic respiratory insufficiency, or acute respiratory infections excluding septic shock;
- Treatment of DVT with or without pulmonary embolism;
- Treatment of unstable angina or non-Q-wave myocardial infarction (MI) (in combination with aspirin); and
- Treatment of acute ST-segment elevation MI, including patients who are to be managed medically as well as those who will require percutaneous coronary intervention.

Prevalent contraindications to enoxaparin in the LTC setting include

- Active bleeding;
- Active gastric or duodenal ulcer;
- Acute or subacute bacterial endocarditis;
- Diabetic or hemorrhagic retinopathy;
- Hemorrhagic cerebrovascular accident (except in the presence of systemic emboli);
- History of confirmed or suspected immunologically mediated heparin-induced thrombocytopenia (HIT; delayed-onset severe thrombocytopenia; see Chapter 11);
- Hypersensitivity to the drug or any of its constituents (including benzyl alcohol, which is found only in the multi-dose formulation), to porcine protein, or to heparin;
- Major blood clotting disorders (e.g., hemophilia, idiopathic thrombocytopenic purpura); and
- Uncontrolled hypertension (above 160/95 mm Hg).

Platelet counts should be measured before initiating treatment with enoxaparin and should be monitored periodically for the duration of treatment. Caution is advised when treating patients with hepatic insufficiency with enoxaparin.

Dalteparin (Fragmin)

Dalteparin is indicated for

- Thromboprophylaxis in patients who have had recent surgery,
- Treatment of acute DVT,
- Treatment of unstable coronary artery disease,
- Prevention of clotting in the extracorporeal system during hemodialysis and hemofiltration in connection with acute renal failure or chronic renal insufficiency,

- Extended treatment of symptomatic venous thromboembolism (VTE) to prevent recurrence in patients with cancer, and
- Reduction in the occurrence of DVT in patients with severely restricted mobility during acute illness.

The following are contraindications to dalteparin:
- Acute gastroduodenal ulcer;
- Cerebral hemorrhage;
- Diabetic or hemorrhagic retinopathy;
- History of confirmed or suspected HIT (delayed-onset severe thrombocytopenia);
- Hypersensitivity to the drug or any of its constituents (including benzyl alcohol), to porcine protein, or to heparin;
- Injury to or surgery involving the central nervous system, eyes, and ears;
- Major blood clotting disorders;
- Other conditions or diseases involving an increased risk of hemorrhage;
- Acute or subacute infective endocarditis;
- Severe uncontrolled hypertension; and
- Uncontrollable active bleeding.

As with enoxaparin, platelet counts should be measured before initiating treatment with dalteparin and twice weekly for the duration of treatment. Thrombocytopenia of any degree should be monitored closely.

Tinzaparin (Innohep)

Tinzaparin is indicated for
- Prevention of postoperative VTE in high-risk patients undergoing orthopedic or general surgery,
- Treatment of DVT or PE, and
- Prevention of clotting in indwelling intravenous lines for hemodialysis and extracorporeal circulation in patients who are not at high risk for bleeding.

Pertinent contraindications to tinzaparin in the LTC setting include
- Acute cerebral insult or hemorrhagic cerebrovascular accident (except in the presence of systemic emboli);
- Acute or subacute infective endocarditis;
- Bleeding from a local lesion such as an acute ulcer (e.g., gastric, duodenal) or ulcerating carcinoma;
- Diabetic or hemorrhagic retinopathy;
- Generalized hemorrhage tendency and other conditions or diseases involving an increased risk of hemorrhage;
- Hemophilia or major blood-clotting disorders;
- History of confirmed or suspected immunologically mediated HIT;
- Hypersensitivity to the medication or to any of its constituents (including benzyl alcohol or sodium bisulfite), to porcine protein, or to heparin or other LMWHs;
- Injury to or surgery involving the central nervous system, eyes, or ears;
- Renal impairment; and
- Uncontrolled severe hypertension.

Because of an increased risk of bleeding, spinal or epidural anesthesia is contraindicated when high (i.e., nonprophylactic) doses of tinzaparin are required.

Measurement of peak anti-Xa levels may be considered when monitoring patients receiving tinzaparin who are at higher risk for bleeding, such as elderly patients.

Specific Cautions Relating to the Use of Low-Molecular-Weight Heparins in the Long Term Care Setting

In the LTC setting, anticoagulation with LMWH is complicated by several important factors: the influence of renal insufficiency on LMWH excretion, the influence of high and low body weights on volume of distribution, and the increased rate of bleeding in elderly patients, especially those aged 80 or older. Careful dosing is advised for these subsets of patients, along with evaluation of the need for concomitant medications, especially antiplatelet agents, in elderly patients with low body weight (below 45 kg) or impaired renal function (CrCl below 30 ml/min).

LMWHs can suppress the adrenal secretion of aldosterone, leading to hyperkalemia. Patients with chronic renal failure or diabetes mellitus and those taking potassium-sparing drugs are at higher risk for this adverse effect. Plasma potassium should be measured periodically in patients at risk.

LMWHs have nearly 100% bioavailability when administered subcutaneously, achieving peak anti-factor-Xa activity in 3 to 5 hours.[2] Laboratory monitoring is usually not needed; however, the half-life of anti-Xa activity following administration of LMWH may be prolonged in the elderly patient population. ACCP 2012 recommends that patients who are receiving treatment doses and who have an estimated CrCl of less than 30 ml/min should receive a reduced dose.[3] When monitoring is indicated, levels should be obtained 4 hours after administration of a subcutaneous dose. The practicality of monitoring anti-factor-Xa activity is limited, however, by the lack of availability of timely anti-factor-Xa testing and the lack of specific data on the minimally effective levels needed to prevent or treat thrombosis.

Dosing of Low-Molecular-Weight Heparin in Renal Insufficiency

Renal insufficiency is a concern when using LMWH because decreased renal excretion may lead to accumulation of anti-factor-Xa and a subsequent increased risk of bleeding; however, the use of unfractionated heparin also presents an increased risk of bleeding in patients with severe renal failure. Thus, for patients with an estimated CrCl of less than 30 ml/min who require full-dose anticoagulation, ACCP 2012 recommends a reduction in the dose of LMWH.[3]

Of particular relevance for practitioners in the LTC setting is the recommendation to consider renal function when selecting anticoagulants and determining doses of antithrombotic agents that are cleared by the kidneys (e.g., direct thrombin inhibitors, fondaparinux, LMWHs) (Grade 2C).[4] It is prudent to use low-dose unfractionated heparin for prophylaxis in severe renal insufficiency (CrCl less than 30 ml/min) (Grade 2C).[5] Therapeutic doses of LMWH in severe renal insufficiency are associated with a 2- to 4-fold increase in risk for major bleeding.[6] In contrast, short-term prophylactic doses of LMWH have not been associated with increased bleeding complications.[7] This observation and studies of renally adjusted enoxaparin suggest that practitioners may use enoxaparin for VTE prophylaxis in patients with an estimated CrCl of less than 30 ml/min if they lower the dose to 30 mg/day.[7]

TABLE 10.1. Dosing of Low-Molecular-Weight Heparins and Fondaparinux for FDA-Approved Indications

Indication	Fondaparinux	Enoxaparin	Dalteparin	Tinzaparin
DVT prophylaxis in abdominal surgery	• 2.5 mg by subcut injection once daily after hemostasis established • Administer initial dose no earlier than 6–8 hr after surgery • Usual duration of therapy 5–9 days (up to 10 days in clinical trials)	40 mg subcut once daily	• 2500 IU subcut once daily ***or*** • 5000 IU subcut once daily ***or*** • 2500 IU subcut followed by 2500 IU subcut 12 hr later, then 5000 IU subcut once daily • Usual duration of therapy 5–10 days	No indication
DVT prophylaxis in knee replacement surgery	• 2.5 mg by subcut injection once daily after hemostasis established • CrCl 30-50 ml/min: Reduce dose by 50% • CrCl below 30 ml/min: Do not use • Usual duration of therapy 5–9 days (up to 11 days in clinical trials)	• 30 mg subcut every 12 hr • CrCl below 30 ml/min: 30 mg subcut once daily	No indication	No indication
DVT prophylaxis in hip replacement surgery	• 2.5 mg by subcut injection once daily after hemostasis established • Usual duration of therapy 5–9 days (up to 11 days in clinical trials) • CrCl 30-50 ml/min: Reduce dose by 50% • CrCl below 30 ml/min: Do not use	• 30 mg subcut every 12 hr ***or*** • 40 mg subcut once daily • CrCl below 30 ml/min: 30 mg subcut once daily	• *Postoperative start:* 2500 IU subcut 4–8 hr after surgery, then 5000 IU subcut once daily ***or*** • *Preoperative start:* 2500 IU subcut 2 hr before surgery followed by 2500 IU subcut 4–8 hr after surgery, then 5000 IU subcut once daily • Usual duration of therapy 5–10 days after surgery (up to 14 days well tolerated in clinical trials)	No indication
DVT prophylaxis in hip fracture surgery	• 2.5 mg by subcut injection once daily after hemostasis established • Usual duration of therapy 5–9 days (up to 11 days in clinical trials)	No indication	No indication	No indication

TABLE 10.1 Continued
Dosing of Low-Molecular-Weight Heparins and Fondaparinux for FDA-Approved Indications

Indication	Fondaparinux	Enoxaparin	Dalteparin	Tinzaparin
DVT prophylaxis in medical patients	No indication	40 mg subcut once daily	5000 IU subcut once daily	No indication
DVT and PE treatment	• Dose by body weight (once daily subcut injection): ○ Below 50 kg: 5 mg ○ 50 to 100 kg: 7.5 mg ○ Over 100 kg: 10 mg • Initiate concomitant treatment with warfarin as soon as possible, usually within 72 hr • Continue treatment with fondaparinux for at least 5 days and until INR 2–3 • Usual duration of administration of fondaparinux 5–9 days (up to 26 days in clinical trials)	No indication	No indication	No indication
Inpatient treatment of acute DVT with or without PE	No indication	• 1 mg/kg subcut every 12 hr ***or*** • 1.5 mg/kg subcut once daily	No indication	175 anti-Xa IU/kg body weight subcut once daily for at least 6 days and until patient is adequately anticoagulated with warfarin (INR at least 2.0 for 2 consecutive days)
Outpatient treatment of acute DVT without PE	No indication	1 mg/kg subcut every 12 hr	No indication	No indication
Unstable angina and non-Q-wave MI	No indication	1 mg/kg subcut every 12 hr (with aspirin)	• 120 IU/kg body weight (to max 10,000 IU) subcut every 12 hr • Concurrent oral aspirin (75–165 mg once daily) recommended unless contraindicated • Continue treatment until patient is clinically stable • Usual duration of therapy 5–8 days	No indication

TABLE 10.1 Continued
Dosing of Low-Molecular-Weight Heparins and Fondaparinux for FDA-Approved Indications

Indication	Fondaparinux	Enoxaparin	Dalteparin	Tinzaparin
Acute STEMI in patients aged less than 75 years (for dosing in subsequent PCI)	No indication	30 mg single IV bolus ***plus*** 1 mg/kg subcut dose followed by 1 mg/kg subcut every 12 hr (with aspirin)	No indication	No indication
Extended treatment of VTE in patients with cancer	No indication	No indication	• 200 IU/kg total body weight subcut once daily for 30 days • Total daily dose should not exceed 18,000 IU	No indication
DVT reduction in medical patients during acute illness	No indication	No indication	• 5000 IU by subcut injection once daily • Usual duration of therapy in clinical trials 12–14 days	No indication

CrCl: creatinine clearance; DVT: deep vein thrombosis; INR: international normalized ratio; IU: international units; IV: intravenous; MI: myocardial infarction; PCI: percutaneous coronary intervention; PE: pulmonary embolism; STEMI: ST-segment elevation myocardial infarction; subcut: subcutaneous; VTE: venous thromboembolism.

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Unfractionated Heparin

Unfractionated heparin (UFH) is frequently used in the LTC setting for thromboembolism prophylaxis and treatment. ACCP 2012 recommends the use of LMWHs over UFH for treatment of VTE in patients with normal renal function; UFH is preferred in patients whose renal function is compromised (CrCl less than 30 ml/min).[13]

UFH can be administered intravenously or subcutaneously; the latter is the more commonly used route of administration in the LTC setting. Intravenous UFH has been identified as a high-risk medication by the Institute of Safe Medication Practices.[14]

Contraindications to UHF use are active bleeding, heparin sensitivity, and thrombocytopenia.

UFH can suppress the adrenal secretion of aldosterone, leading to hyperkalemia. Patients with chronic renal failure or diabetes mellitus and those taking potassium-sparing drugs are at higher risk for this adverse effect. Plasma potassium should be measured periodically in patients at risk.

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11. HEPARIN-INDUCED THROMBOCYTOPENIA

Heparin-induced thrombocytopenia (HIT) is an immune-mediated drug reaction. It is a clinicopathological syndrome that entails immune complex formation and thrombocytopenia.[1,2] Heparin can induce two types of thrombocytopenia: non–immune-mediated heparin-associated thrombocytopenia (previously called type I HIT), and immune-mediated thrombocytopenia, now referred to as HIT (formerly referred to as type 2 HIT). The distinction between the two types is important.

Non–immune-mediated heparin-associated thrombocytopenia occurs in 10% to 30% of patients receiving heparin and presents a low risk of thrombosis. It occurs within 5 days of heparin administration, is usually associated with platelet counts greater than 100,000, and will resolve with continued administration of heparin.[3]

Immune-mediated HIT, on the other hand, occurs in 2% to 3% of patients after 5 days of heparin therapy, is associated with arterial and venous thrombosis, and is typically associated with platelet counts below 150,000 (or a greater than 50% decline from pretreatment levels). Unlike non–immune-mediated heparin-associated thrombocytopenia, HIT will ***not*** resolve with continued administration of heparin; thus, a change to alternative anticoagulants is required.[3]

The underlying pathophysiology of HIT is the formation of antibodies against a heparin and platelet factor 4 (PF4) complex.[4] HIT may initially present as isolated thrombocytopenia. If it is untreated, platelet aggregation can lead to arterial and venous thrombi that can result in organ loss and death.

Some authors distinguish between two clinical patterns of HIT: immune-mediated thrombocytopenia without thrombosis, or isolated HIT, and immune-mediated thrombocytopenia with clinically evident thrombosis, or HIT with thrombosis (HITT). Because these two presentations share the same pathophysiology, the principles of treatment are the same for both.[3]

Epidemiology

The true number of HIT cases in the United States is unknown. In retrospective studies, its frequency among patients exposed to heparin for more than 4 days ranges from 0.2% to 5%.[5,6] Although rates of HIT are relatively low, some sobering facts attest to the clinical importance of this syndrome: approximately 12 million patients are exposed to heparin products each year in the United States.[7] Prospective studies have estimated the incidence of heparin-induced antibodies to the heparin/PF4 complex at around 14%, whereas only 5% of patients develop thrombocytopenia.[8] A study of 108 hospitalized patients diagnosed with HIT showed that a severe fall in platelet counts in elderly patients receiving heparin appeared to be associated with a higher risk for developing HIT.[9] Patients undergoing cardiac or orthopedic surgery or other surgeries causing significant inflammatory processes have a higher risk for developing HIT compared with medical or obstetric patients.[10]

Screening

Recommendations to screen for HIT are based on patients' risk. In patients whose risk for developing HIT is greater than 1%, ACCP 2012 recommends that platelets be monitored every 2 to 3 days from days 4 to 14 (or until heparin is stopped) (Table 11.1) (Grade 2C). In practice, platelet monitoring is indicated only if heparin is administered to postoperative patients who have received prophylactic or therapeutic doses of heparin and those who have had cardiac surgery.

In patients who have been exposed to heparin in the past 100 days who are restarted on heparin products, obtain a platelet count before restarting heparin and 24 hours after restarting heparin.[1]

TABLE 11.1. Incidence of Heparin-Induced Thrombocytopenia by Type of Heparin Exposure and Patient Population

Patient Population (minimum of 4-day exposure to heparin)	Incidence of HIT (%)
Medical	
Patient with cancer	1
Heparin, prophylactic or therapeutic dose	0.1–1
LMWH, prophylactic or therapeutic dose	0.6
Intensive-care patients	0.4
Heparin flushes	less than 0.1
Postoperative Patients	
Heparin, prophylactic dose	1–5
Heparin, therapeutic dose	1–5
Heparin flushes	0.1–1
LMWH, prophylactic or therapeutic dose	0.1–1
Cardiac-surgery patients	1–3

HIT: heparin-induced thrombocytopenia; LMWH: low-molecular-weight heparin.

Adapted from Linkins et al, 2012[1]

Recognition

HIT has three recognized patterns of onset: *typical, rapid,* and *delayed*.[11] When HIT is suspected, a rapid, thorough assessment should be ensured as 15% of patients experience subsequent amputation and 4% to 30% of affected patients die. Strongly consider urgent consultation with a hematologist, and quickly begin appropriate workup and treatment.[7]

Typical onset HIT is the most common pattern; it progresses from platelet antibody formation to an unexplained drop of 30% to 50% in platelet count on day 5 to 10 of heparin therapy, and from there to thrombocytopenia (either a 50% or greater relative drop in platelets or a platelet count of less than 150,000) on day 7 to 14. As discussed above, HIT may or may not be accompanied by systemic thrombosis.

Rapid-onset HIT is an abrupt drop in platelet count (within 24 hours) in patients with prior exposure to heparin. This pattern of onset is seen in 25% of cases.[1] In the literature, the time frame for prior heparin exposure is described as within the past 100 days. Patients may experience systemic symptoms 5 to 30 minutes after administration of a heparin bolus.

In *delayed-onset* HIT, thrombocytopenia and thrombosis occur several days to 3 weeks after heparin is stopped.[11] This pattern of onset is seen in 3% to 5% of cases.

HIT should be suspected if a patient treated with heparin develops any of the following symptoms that cannot be otherwise explained:

- 30% to 50% proportional drop in platelet count,
- Thrombosis (even without the presence of thrombocytopenia), or
- Thrombocytopenia with thrombosis.

Thrombocytopenia is the most common clinical manifestation of HIT, occurring in 85% to 90% of all patients. In up to 25% of cases, however, thrombosis is found to have preceded thrombocytopenia. Lower-limb venous thrombosis is thereby the most common clinical presentation of HIT, and pulmonary embolism the most common life-threatening complication.[12]

For patients at risk for HIT, a variety of signs and symptoms of venous or arterial occlusion should raise clinical suspicion.[13] These signs may include skin or limb cyanosis, local erythema, pain, and swelling. Patients can present with dyspnea, hypoxia, or chest pain that is pleuritic, cardiac, or ischemic in nature. Minor deteriorations in mental status and focal neurological deficits can signal cerebrovascular ischemia. Abdominal pain, otherwise unexplained metabolic acidosis, and leukocytosis can suggest the presence of mesenteric ischemia. Flank or abdominal pain can suggest adrenal hemorrhagic necrosis, which, if bilateral, can lead to shock (adrenal crisis) that may respond to treatment with corticosteroids. HIT-induced skin lesions can present as skin necrosis or as erythematous plaques at heparin injection sites. Arterial thrombotic events are less common than venous events, occurring in 3% to 10% of cases.

A relatively uncommon presentation of HIT is an acute systemic reaction that begins 5 to 30 minutes after administration of an intravenous heparin bolus.[12] An acute systemic reaction may include cardiac arrest, chest pain, chill or rigors, diarrhea or vomiting, dyspnea, fever, flushing, headache, hypertension, nausea, tachycardia, tachypnea, or transient amnesia.

Assessment

A patient with suspected HIT should receive immediate attention. A management decision should be made immediately because the rate of thrombosis prior to treatment is approximately 5% per day.[14] A physical examination should include vital signs, pulse oximetry, and assessment for physical findings suggestive of an arterial or venous thrombosis.

Next, one must determine the pretest probability of HIT (Table 11.2). Pretest probability is based on the degree of thrombocytopenia, timing of platelet reduction, occurrence of thrombosis or other clinical manifestations of HIT, and determination of whether thrombocytopenia might have another cause.[15] A score of 0 to 3 indicates low risk of HIT; 4 to 5, moderate risk; and 6 to 8, high probability of HIT. Among patients with high pretest probability, HIT is confirmed in 24% to 68% of patients. Rates of HIT among patients with low probability scores range from 0% to 3%. In practice, the pretest probability of HIT is moderate or high for patients receiving heparin who develop thrombocytopenia or a new thrombosis on days 5 to 10 of heparin therapy.[16]

TABLE 11.2. Estimating the Pretest Probability of Heparin-Induced Thrombocytopenia

Event	Points*		
	2	1	0
Thrombocytopenia	• Fall in platelet count of greater than 50% ***or*** • Nadir more than 20,000/μL†‡	• Platelet count fall 30%–50% ***or*** • Nadir 10,000–19,000/μL ***or*** • Platelet count fall greater than 50% directly resulting from surgery	• Platelet count fall less than 30% ***or*** • Nadir less than 10,000/μL
Timing of platelet count fall or other sequelae	• Clear onset between days 5–10, ***or*** • Onset for more than 1 day (if heparin exposure in past 30 days)	• Consistent with immunization but not clear (e.g., missing platelet counts) ***or*** • Thrombocytopenia onset after day 10 ***or*** • Onset for less than 1 day (if heparin exposure in past 31–100 days)	Platelet count fall too early (without recent heparin exposure)
Thrombosis or other sequelae (e.g., skin lesions)	• New thrombosis, ***or*** • Skin necrosis at heparin injection sites, ***or*** • ASR after IV heparin bolus	• Progressive or recurrent thrombosis ***or*** • Erythematous skin lesions ***or*** • Suspected thrombosis not yet proven	None
Other causes for thrombocytopenia	No other evident cause for platelet count fall	Possible other cause is evident	Definite other cause is present

ASR: acute systemic reaction; HIT: heparin induced thrombocytopenia; IV: intravenous.

*Points 0,1, or 2 for each of four categories; maximum score possible is 8. A score of 6–8 = high; 4–5 = intermediate; 0–3 = low.

†The first day of immunizing heparin exposure is considered day 0; the day the platelet count begins to fall is considered the day of onset of thrombocytopenia. (It generally takes 1 to 3 more days to pass the arbitrary threshold that defines thrombocytopenia.)

‡Platelet counts of less than 20,000 are rare in HIT. In the absence of other clinical criteria for HIT, lower platelet counts are less likely to be caused by HIT.

The author acknowledges the contribution of Professor Ben H. Chong (Chairman, Platelet Immunology Scientific and Standardization Committee, International Society on Thrombosis and Haemostasis) in initiating this discussion toward developing a scoring system that takes into account clinical and laboratory criteria in arriving at a diagnosis of HIT.

Adapted from Warkentin et al, 2003[15]

Management

When HIT is suspected, the essential first step is to immediately discontinue all heparin products. Discontinuation of heparin removes the ongoing stimulus for antibody production, but does not treat the hypercoagulable state.[17] If HIT is a plausible diagnostic possibility, the risk of subsequent symptomatic thrombosis and death is high, even if no thrombosis is apparent at the time HIT is suspected (i.e., isolated HIT). Thus, the next step after discontinuing heparin is to transfer the patient to the hospital for urgent evaluation and treatment. If feasible, the practitioner should inform the receiving hospital about the patient's presenting symptoms and laboratory findings.

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12. PERIOPERATIVE MANAGEMENT OF ANTITHROMBOTIC THERAPY

Table 12.1 presents ACCP 2012's modified recommendations for interrupting and resuming antithrombotic therapy before and after surgical procedures.

TABLE 12.1. ACCP Recommendations for Perioperative Management of Antithrombotic Therapy

Type of Procedure	Recommendation		Strength of Recommendation
Interruption/Resumption of Warfarin			
Minor surgery Dental procedures	Continue warfarin with co-administration of pro-hemostatic agent OR stop warfarin 2-3 days prior to procedure		2C
Dermatological procedures	Continue warfarin around the time of the procedure and optimize local hemostasis		2C
Cataract surgery	Continue warfarin around the time of surgery		2C
Major surgery	• Stop warfarin 5 days prior to surgery		1C
	• Resume warfarin approx. 12-24 h after surgery and when hemostasis is adequate		2C
	For patients with mechanical heart valves, atrial fibrillation, or venous thromboembolism		
	At **high** risk for thromboembolism	Bridging anticoagulation with heparin is suggested	2C
	At **moderate** risk for thromboembolism	Decision to use or not use bridging anticoagulation should be based on an assessment of individual patient- and surgery-related factors	–
	At **low** risk for thromboembolism	**No** bridging anticoagulation is suggested	2C
Interruption/Resumption of Aspirin			
Minor surgery Dental surgery Dermatologic surgery Cataract surgery	For patients receiving aspirin for secondary prevention of cardiovascular disease	• **Continue** aspirin around the time of surgery • **Do not** stop aspirin 7-10 days prior to minor surgery	2C
Major surgery	For patients receiving aspirin who are at **moderate to high risk** for a cardiovascular event and require noncardiac surgery	**Continue** aspirin around the time of surgery	2C

Adapted from: Douketis et al 2012[1]

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APPENDIX 1. Thrombosis Risk Assessment

Add 1 point for each of the following risk factors:

- ☐ Aged 41–60
- ☐ Minor surgery planned
- ☐ History of major surgery within 1 mo
- ☐ Varicose veins
- ☐ History of inflammatory bowel disease
- ☐ Current leg swelling
- ☐ BMI higher than 25
- ☐ Acute MI
- ☐ CHF within 1 mo
- ☐ Sepsis within 1 mo
- ☐ Serious lung disease, including pneumonia, within 1 mo
- ☐ Abnormal pulmonary function (COPD)
- ☐ Medical patient on bed rest

Add 3 points for each of the following risk factors:

- ☐ Aged over 75
- ☐ History of DVT/PE
- ☐ Family history of thrombosis
- ☐ Positive Factor V Leiden
- ☐ Positive prothrombin 20210A
- ☐ Elevated serum homocysteine
- ☐ Positive lupus anticoagulant
- ☐ Elevated anticardiolipin antibodies
- ☐ HIT
- ☐ Other congenital or acquired thrombophilia

Add 2 points for each of the following risk factors:

- ☐ Aged 60–74
- ☐ Arthroscopic surgery
- ☐ Malignancy (present or previous)
- ☐ Major surgery (more than 45 min)
- ☐ Laparoscopic surgery more than 45 min
- ☐ Patient confined to bed more than 72 h
- ☐ Immobilizing plaster cast less than 1 mo
- ☐ Central venous access

Add 5 points for each of the following risk factors:

- ☐ Elective lower extremity arthroplasty
- ☐ Hip, pelvis, or lower extremity arthroplasty
- ☐ Stroke within 1 mo
- ☐ Multiple trauma within 1 mo
- ☐ Acute spinal cord injury (paralysis) within 1 mo

For women only

Add 1 point for each of the following risk factors:

- ☐ Oral contraceptives or hormone replacement therapy
- ☐ Pregnancy or postpartum less than 1 mo
- ☐ History of unexplained stillborn infant, at least 3 recurrent spontaneous abortions, premature birth with toxemia, or growth-restricted infant

Total Risk Factor Score: _____

BMI: body mass index; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; DVT: deep vein thrombosis; HIT: heparin-induced thrombocytopenia; MI: myocardial infarction; PE: pulmonary embolism.

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APPENDIX 2. Prophylaxis Regimen Based on Risk-Factor Total

Total Risk Factor Score	Incidence of DVT	Risk Level	Prophylaxis Regimen
0–1	less than 10%	Low	No specific measures; early ambulation
2	10%–20%	Moderate	ES or IPC or LDUH or LMWH
3–4	20%–40%	High	IPC or LDUH or LMWH alone or combined with ES or IPC
5 or higher	40%–80%, 1%–5% mortality	Highest	LDUH or LMWH or Factor Xa inhibitor combined with ES or IPC

ES: elastic stockings; IPC: intermittent pneumatic compression; LDUH: low-dose unfractionated heparin; LMWH: low molecular weight heparin.

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APPENDIX 3. Prophylaxis Safety Considerations

Anticoagulants: Factors Associated With Increased Bleeding*

☐ Is patient experiencing any active bleeding?
☐ Does patient have a current or past history of heparin-induced thrombocytopenia?
☐ Is patient taking oral anticoagulants or platelet inhibitors (aspirin, clopidogrel, dipyridamole, NSAIDs)?
☐ Is patient's creatinine clearance abnormal? Record value _____

Intermittent pneumatic compression (IPC)†

☐ Does patient have severe peripheral arterial disease?
☐ Does patient have congestive heart failure?
☐ Does patient have superficial or deep vein thrombosis?

NSAIDs: nonsteroidal anti-inflammatory drugs.

* If any of the risk factors are present, the patient may not be a candidate for anticoagulant therapy. Consider alternative prophylactic measures.

† If any of the risk factors are present, the patient may not be a candidate for IPC therapy. Consider alternative prophylactic measures.

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APPENDIX 4. Baseline Anticoagulant Risk/Benefit Assessment

Patient Name_____ Date_____

Height		Weight		Creatinine	
Estimated GFR		INR		Stool guaiac	
Urine dip for blood		Hemoglobin		Platelet count	
Stool *H. pylori* antigen (optional)		Blood glucose			

Estimated Stroke Risk for Patients With Atrial Fibrillation (Adapted from Gage et al, 2001[1])		
CHADS-2 Score	Strokes/10,000 patients/y	1 point for **C**ongestive heart failure or ejection fraction less than 50% **H**ypertension **A**ged 75 or older **D**iabetes 2 points for **S**troke or TIA
0	190	
1	280	
2	400	
3	590	
4	850	
5	1,250	
6	1,820	

Benefits of Warfarin Therapy (Adapted from Singer et al, 2004[2])

☐ Risk of stroke decreased 65%

☐ Stroke less likely to cause death or severe disability if taking warfarin

Absolute Contraindications to Warfarin (Adapted from Man-Son-Hing, Laupacis, 2003[3])

☐ Current active bleeding

☐ Blood pressure consistently above160/90

☐ Platelet count less than 50,000

☐ Noncompliance with medication or monitoring

Relative Contraindications to Warfarin (Adapted from Man-Son-Hing, Laupacis, 2003[3])

☐ Ethanol 2 oz/day[3] or more

☐ Extreme functional disability

☐ Nonselective NSAID without gastric cytoprotection (e.g., PPI, misoprostol)[3]

☐ Poor short-term prognosis due to malignancy, advanced chronic disease

Intracerebral Bleeding Risk for Outpatients With Atrial Fibrillation (per 10,000 patients/y) (Adapted from Levine et al, 2004[4])	
No therapy: 10 ICH; 4 will die	Warfarin: 75 ICH; 43 will die
Aspirin: 20 ICH; 5 will die	
Subdural Hematoma Risk in Outpatient Elderly (per 10,000 people/y) (Adapted from Man Son Hing et al, 1999[5])	
No therapy: 4 SDH; 2 will die	Aspirin: 8 SDH; 4 will die
Warfarin: 12 SDH; 4 will die	
Risk of Hospitalization for Central Nervous System Bleeding Among Nursing Home Stroke Survivors (Adapted from Quilliam et al, 2001[6])	
Aspirin: 19/10,000 people/y	Warfarin; 33/10,000 people/y

Relative Risks of Significant Gastrointestinal Bleeding (Adapted from Man Son Hing, Laupacis, 2003; 2002[3,7])	
☐ History of active peptic or duodenal ulcer bleeding[2]	30% chance of rebleeding in 5 y; 13.5 times excess risk compared to those with negative PMH
	No increased risk if treated for *H. pylori*
☐ Taking NO warfarin, aspirin, NSAID[6]	RR 1; 117 upper-GI bleed/10,000 people/y (16 will die)
☐ Taking warfarin[6]	RR 2.4; 280 upper-GI bleed/10,000 people/y (42 will die)
☐ Taking aspirin[6]	RR 1.2; 140 upper-GI bleed/10,000 people/y (7 will die)
☐ Taking nonselective NSAID[6]	RR 3.8; 450 upper -GI bleed/10,000 people/y
☐ Taking COX-2 selective NSAID[6]	RR 1.9; 320 upper-GI bleed/10,000 people/y
☐ Taking PPI or misoprostol with NSAID[6,7]	RR 1.9; 320 upper-GI bleed/10,000 people/y

APPENDIX 4. Baseline Anticoagulant Risk/Benefit Assessment (continued)

Conditions That May Increase Bleeding Risk and Require More Frequent Monitoring[4,8]

- ☐ Prior stroke[3]
- ☐ Liver disease[3]
- ☐ Serum creatinine more than 1.5 mg/dL[7]
- ☐ Aged 65 or older[7]
- ☐ Malignancy[3]
- ☐ Malnutrition[3]
- ☐ Diabetes[7]
- ☐ Recent MI[7]
- ☐ GFR less than 30[3]
- ☐ Hematocrit less than 30%[7]

AF: atrial fibrillation; COX-2: cyclooxygenase 2 inhibitor; GFR: glomerular filtration rate; GI: gastrointestinal; ICH: intracerebral hemorrhage; INR: international normalized ratio; MI: myocardial infarction; NSAID: nonsteroidal anti-inflammatory drug; PPI: proton pump inhibitor; PMH: past medical history; RR: relative risk; SDH: subdural hematoma; TIA: transient ischemic attack.

Adapted with permission from William D. Smucker, MD, CMD, Medical Director, Altenheim Nursing Home, Strongsville, Ohio.

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APPENDIX 5. Sample Facility Policy on Safe and Effective Warfarin Use

Purpose: To assure safe and effective use of warfarin in all facility patients.

Policy:

- ***Patient identification***
  Charts of patients receiving warfarin will be labeled in a way that makes them easily identifiable to nursing staff.

- ***INR reporting***
  - Nursing staff will record pertinent information about a patient's clinical status, medication regimen, and lab reports to attending physician or licensed designee.
  - Nurse is responsible for assuring that an order is obtained and recorded for a subsequent INR each time an INR value is reported to a practitioner.

- ***INR testing frequency***
  - Patients receiving warfarin will have an INR tested at least every 4 weeks.
  - Testing may occur more frequently depending on the clinical situation.

- ***Antibiotic therapy***
  - If antibiotics are prescribed for a patient taking warfarin, the nurse will contact the attending physician for recommendations about INR testing frequency.
  - Practitioners may use the *Facility Recommendations for Warfarin Dosing and Monitoring While on Antibiotics* (see below).

- ***Surgical treatment or invasive procedures***
  - If a surgical procedure is planned, the nurse will notify the attending physician of the planned procedure.
  - The nurse will contact the clinician performing the procedure and record detailed information about that clinician's recommendations regarding perioperative anticoagulation and will communicate these recommendations to the attending physician.

- ***Change in medication regimen***
  When a change occurs in the dose of a medication prescribed to a patient, when a medication is stopped, or when a new medication is added to the patient's regimen, the nurse should contact the attending physician and request that an INR be performed 1 week after the change in medication regimen.

- ***INR quality assurance: Laboratory audit***
  Nursing staff will perform weekly audits of INR tests ordered and completed.

Procedures:

- ***Reporting INR values to practitioner***
  When an INR value arrives, the nurse will prepare for practitioner notification using the *Practitioner INR Notification Template* (Appendix 8). In addition, the nurse should have available for reference
  - *Warfarin/INR Flow Sheet* (Appendix 7)
  - Telephone Order Sheet

- ***Recording practitioner notification and new orders***
  After notifying the practitioner and receiving orders, the nurse will record the following information on the Telephone Order Sheet:
  - Practitioner notified (e.g., "INR value reported to Dr. Jones")
  - Action taken (e.g., "Continue TWD, 5 mg warfarin x 2 days"; "Hold warfarin")
  - Order next INR (e.g., INR 12-01-2012) (For every INR notification, a follow-up INR ***must*** be scheduled within no more than 4 weeks)
  - Other information as appropriate (e.g., hold warfarin until INR reaches a specified value; notify practitioner if INR is greater or less than a specified value)

- ***Updating INR Flow Sheet***
  - Record appropriate information on Warfarin/INR Flow Sheet.
  - Fax updated flow sheet to practitioner.

- ***INR quality assurance : Laboratory audit***
  Director of Nursing will designate a staff person to audit that INRs were drawn as ordered and that orders for follow-up INRs were submitted to and received by the lab.
  - Print lab list of INRs due in upcoming week.
  - Use this list to confirm that each INR was completed.
  - Use this list to confirm that a date for next INR is recorded in telephone orders.
  - Contact lab to confirm that order for next INR has been received and recorded.
  - Submit list to DON or designee for quality improvement/quality assurance records.

Facility Recommendations for Warfarin Dosing and Monitoring While on Antibiotics

- Whenever a patient receiving warfarin is placed on antibiotics, contact the practitioner for monitoring and dosing orders.
- The practitioner may
  - Recommend an individualized plan for checking INR more frequently while the patient is receiving antibiotics, or
  - Follow *Facility Recommendations for INR Testing During Antibiotic Therapy* (below).

Facility Recommendations for INR Testing During Antibiotic Therapy

- Check INR at initiation of antibiotic therapy.
- Give usual warfarin dose and check INR every other day while the patient remains on antibiotics.
- Check INR 5–7 days after discontinuation of antibiotics.

DON: Director of Nursing; INR: international normalized ratio; TWD: total weekly dose.

Adapted with permission from William D. Smucker, MD, CMD, Medical Director, Altenheim Nursing Home, Strongsville, Ohio.

APPENDIX 6. Guide to Starting Warfarin in Elderly Patients

Initiation Algorithm 1: 4 mg doses

- Give warfarin dose at 6 p.m.
- Measure INR in a.m.
- Give UFH or LMWH concomitantly, if indicated, during warfarin titration.

Dosing algorithm

1. On Days 0, 1, and 2, administer 4 mg warfarin.
2. Measure INR on Day 3 to determine predicted daily warfarin dose.
3. Administer predicted warfarin dose daily, measuring INR at least every 2 days until maintenance dose is determined.
4. Maintenance dose is the dose that achieves an INR of no less than 2.0 and not greater than 3.0 on two determinations 48–72 hr apart, with no change in dose for at least 4 days.

TABLE A-6.1. Warfarin Initiation for Elderly Patients: Algorithm 1

Day	INR Value	Warfarin Dose
0	Do not measure	4 mg
1	Do not measure	4 mg
2	Do not measure	4 mg
		Predicted daily warfarin dose
3	INR below 1.3	5 mg
	INR 1.4–1.5	4 mg
	INR 1.6–1.7	3 mg
	INR 1.8–1.9	2 mg
	INR 2.0-2.5	1 mg
	INR above 2.5	Measure INR daily until above 2.5, then give 1 mg

Adapted from: Siguret V, Gouin I, Debray M, et al. Initiation of warfarin therapy in elderly medical inpatients: A safe and accurate regimen. Am J Med 2005; 118(2): 137-142.

Initiation Algorithm 2: 5 mg doses

- Give warfarin dose at 6 p.m.
- Measure INR in a.m.
- Give UFH or LMWH concomitantly, if indicated, during warfarin titration.
- Monitor INR daily and adjust dose accordingly.

Dosing algorithm

Day 1
Warfarin 5 mg

Day 2
INR below 1.5: warfarin 5 mg
INR 1.5–1.9: warfarin 2.5 mg
INR 2.0–2.5: warfarin 1–2.5 mg
INR above 2.5: no warfarin

Day 3
INR below 1.5: warfarin 5–10 mg
INR 1.5–1.9: warfarin 2.5–5 mg
INR 2.0–3.0: warfarin 0–2.5 mg
INR above 3.0: no warfarin

Day 4
INR below 1.5: warfarin 10 mg
INR 1.5–1.9: warfarin 5–7.5 mg
INR 2.0–3.0: warfarin 0–5 mg
INR above 3.0: no warfarin

Day 5
INR below 1.5: warfarin 10 mg
INR 1.5–1.9: warfarin 7.5–10 mg
INR 2.0–3.0: warfarin 0–5 mg
INR above 3.0: no warfarin

Day 6
INR below 1.5: warfarin 7.5–12.5 mg
INR 1.5–1.9: warfarin 5–10 mg
INR 2.0–3.0: warfarin 0–7.5 mg
INR above 3.0: no warfarin

LMWH: low-molecular weight heparin; UFH: unfractionated heparin.

Adapted from Carnahan W, Bracikowski J. Warfarin: Less may be better. Ann Intern Med 1997; 127(4): 332-333.

APPENDIX 7. Sample Warfarin/INR Flow Sheet

Patient		**Attending Physician:**	

DIAGNOSIS (Circle one)	**INR GOAL/RANGE** (Circle one)	**TREATMENT DURATION** (Circle one)	**STOP DATE**
Atrial fibrillation DVT/PE Mechanical Heart Valve	2-3 2-2.5 2.5-3.5	Lifetime 3 months 6 months	_____

Date	**Current INR**	**Current Total Weekly Dose (TWD)**	**BACKGROUND** Antibiotic treatment Recent dose change Missed doses New medication New diet Signs of bleeding, excessive bruising	**ACTION** Hold warfarin until _____ Give Vitamin K Change dose No change Check CBC	**New TWD** (amount & start date)	**Next INR Check Date**	**Nurse**

Use a new row for each action (e.g., holding a dose, every-other-day dose, Vitamin K) or each phone call to practitioner. Record practitioner action. If new dose is ordered, record new TWD and date to start new TWD.

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APPENDIX 8. Practitioner INR Notification Template

The nurse who is notifying the practitioner about a patient's INR may wish to use this template as a checklist to guide the conversation.

Patient name _____ Date_____

Practitioner notified _____

Background

Warfarin indication: ___ Atrial fibrillation ___ DVT/PE ___ Mechanical valve

Duration of warfarin: ____ Lifetime Stop date _____

INR goal : ___ 2.0–3.0 ___ 2.5–3.5 ___ 2.0–2.5

Changes since last INR:

Missed doses of warfarin	____ yes	____ no
New medications	____ yes	____ no
Change in diet	____ yes	____ no
Bleeding	____ yes	____ no

Today's INR _____

Current Total Weekly Dose (TWD) of warfarin (Coumadin) _____

Most recent change in TWD _____

ACTION

Continue current TWD
Give supplemental dose of warfarin _____
Hold warfarin until _____
Give oral Vitamin K ___ 2.5 mg ___5 mg
Begin new TWD dose of _____

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
_____ mg	_____ mg	_____ mg	_____ mg	_____ mg	_____ mg	_____ mg

Next INR due on _____

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APPENDIX 9. INR-Based Guide for Warfarin Monitoring and Dose Adjustment to Maintain Target INR 2.0–3.0

INR below 2.0

Check *Warfarin/INR Flow Sheet* (Appendix 7) to determine if patient suffered an acute DVT or PE within past 3 mo.

INR below 1.5

Scenario A: If patient has had a DVT or PE within 3 mo ***and*** INR is below 1.5

- Contact attending physician to determine if patient requires heparin or LMWH until INR is therapeutic.

Scenario B: If no DVT or PE within 3 mo ***and*** INR is below 1.5

- Contact attending physician to choose from recommended options below ***or*** choose patient-specific plan for dosing and monitoring.

Option 1

If no DVT or PE within 3 mo ***and***

- o **Last 3 INRs between 2.0 and 3.0** ***and***
- o ***No*** recent missed dose, acute illness, dietary change, new medicine or medicine dose

- Continue current dose and recheck INR in 1 wk

Option 2

If no DVT or PE within 3 mo ***and*** no recent missed dose, acute illness, dietary change, new medicine or medicine dose

- Increase TWD by
  - o 2.5 mg/wk if TWD is between 17.5 and 45 mg
  - o 1 mg/wk if TWD is between 4 and 17 mg
- Check INR 1 in wk after starting new TWD

INR 1.5–1.9

Scenario A: If patient has had a DVT or PE within 3 mo

- Contact attending physician to choose from recommended options below ***or*** choose patient specific plan for dosing and monitoring.

Option 1

Continue current TWD and recheck INR in 3–7 days

Option 2

- Increase TWD by
  - o 2.5 mg/wk if TWD is between 17.5 and 45 mg
  - o 1 mg/wk if TWD is between 4 and 17 mg
- Check INR 1 in wk after starting new TWD

Scenario B: If no DVT or PE within 3 mo ***and*** patient's INR values have consistently been in therapeutic range without need for dose adjustment for at least 3 mo

- Continue current TWD and check INR in 1–2 wk

INR above 2.0

INR 2.0–3.0

Scenario A: If patient has had a DVT or PE within 3 mo, choose one of the recommended options below.

Option 1

If ***at least*** two of patient's most recent INRs have ***not*** been between 2.0 and 3.0

- Check INR in 1 wk

Option 2

If patient had one of the following: recent missed dose, acute illness, dietary change, new medicine or medicine dose, or change in TWD

- Check INR in 1 wk ***or*** contact attending physician for patient-specific plan for dosing and monitoring

APPENDIX 9. INR-Based Guide for Warfarin Monitoring and Dose Adjustment to Maintain Target INR 2.0–3.0 (continued)

Scenario B: If patient has had a DVT or PE within 3 mo ***and*** 2 consecutive INRs in therapeutic range
- Recheck INR in 2–4 wk

Scenario C: If no DVT or PE within 3 mo ***and*** patient's INR values have consistently been in therapeutic range without need for dose adjustment for at least 3 mo
- Recheck INR in 4-12 wk

INR 3.1–3.5

Scenario A: If patient has had a DVT or PE within 3 mo
- Hold one warfarin dose and check INR in 1–3 days
- When subsequent INR is 3.0 or below
  - Resume current TWD and recheck INR in 3–7 days

Scenario B: If no DVT or PE within 3 mo

Option 1

If **last three INR values have been between 2.0 and 3.0** ***and*** patient has ***not*** had a recent missed dose, acute illness, dietary change, new medicine or medicine dose
- Continue current dose and recheck INR in 1 wk

Option 2
- Decrease TWD by
  - 2.5 mg/wk if TWD is between 17.5 and 45 mg
  - 1 mg/wk if TWD is between 4 and 17 mg
- Recheck INR in 3–7 days, then weekly for 2 wk

INR 3.6–5.0
- Hold warfarin and check INR in 1–3 days and until INR below 3.0
- Decrease TWD by
  - 2.5 mg/wk if TWD is between 17.5 and 45 mg
  - 1 mg/wk if TWD is between 4 and 17 mg
- Recheck INR in 3–7 days, then weekly for 2 wk

Recommendations for Actions if INR is Above 5.0
- Obtain vital signs, if possible
- Evaluate patient for signs or symptoms of bleeding

If INR is above 5.0 and patient is bleeding
Note: **Contact attending physician for verbal order to confirm options**

- Contact practitioner immediately if bleeding is seen or reported
- Consider immediate hospital transfer if signs of **life-threatening hemorrhage** are seen:
  - Systolic blood pressure less than 100 mmHg
  - Heart rate greater than 100 beats/min
  - Brisk bleeding
  - Decreased level of consciousness
  - Respiratory distress
- If bleeding is not life-threatening and patient is stable, contact attending physician for further orders

APPENDIX 9. INR-Based Guide for Warfarin Monitoring and Dose Adjustment to Maintain Target INR 2.0–3.0 (continued)

If INR is above 5.0 and patient is not bleeding

INR 5.0–9.0

Contact attending physician to choose one of the recommended options below

Option A

- Hold warfarin and check INR every 1–2 days until at or below 3.0
- When INR is at or below 3.0, decrease TWD by
  - 2.5 mg/wk if TWD is between 17.5 and 45 mg
  - 1 mg/wk if TWD is between 4 and 17 mg
- Check INR 1 wk after starting new TWD

Option B

- Give 2.5 mg oral vitamin K (1/2 of 5-mg tablet)
- Hold warfarin and check INR daily until INR below 3.0
- If repeat INR is 4.0 or above after 24 hr, may repeat 2.5 mg dose of vitamin K
- When INR is at or below 3.0, decrease TWD by
  - 2.5 mg/wk if TWD is between 17.5 and 45 mg
  - 1 mg/wk if TWD is between 4 and 17 mg
- Check INR 1 wk after starting new TWD

INR above 9.0

- Give 5 mg oral vitamin K
- Hold warfarin and check INR daily until INR below 3.0
- If repeat INR is 4.0 or above after 24 h, may administer 2.5 mg of oral vitamin K
- When INR is at or below 3.0, decrease TWD by
  - 2.5 mg/wk if TWD is between 17.5 and 45 mg
  - 1 mg/wk if TWD is between 4 and 17 mg
- Check INR 1 wk after starting new TWD

TWD: total weekly dose.

Adapted from:

Ageno W, Gallus AS, Wittkowsky A, et al. Oral anticoagulant therapy: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012; 141(2 Suppl): e44S-88S.

Holbrook A, Schulman S, Witt DM, et al. Evidence-based management of anticoagulant therapy: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141:e152S-e184S.

Horton JD, Bushwick BM. Warfarin therapy: Evolving strategies in anticoagulation. Am Fam Physician 1999; 59(3): 635-646. Review. Erratum in: Am Fam Physician 1999; 60: 1333. Am Fam Physician 2002; 65(2): 172.

TABLE A-9.1. Guide for Warfarin Monitoring and Dose Adjustment

TWD Using 5-mg Tablets								Dosage Adjustments (see previous page)
Day 1	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**TWD**	
0.5 tab	0.5 tab	0.5 tab	0.5 tab	0.5 tab	0.5 tab	0.5 tab	**17.5 mg**	**INR below 2.0** Increase TWD by • 2.5 mg/wk if current TWD is between 17.5 and 45 mg • 1 mg/wk if TWD is between 4 and 17 mg **INR 3.1–3.5** Decrease TWD by • 2.5 mg/wk if current TWD is between 17.5 and 45 mg • 1 mg/wk if current TWD is between 4 and 17 mg **INR 3.6–5.0** Decrease TWD by • 2.5 mg/wk if TWD is between 17.5 and 45 mg • 1 mg/wk if TWD between 4 and 17 mg **INR above 5.0** See ***Recommendations for Actions if INR above 5*** on previous page.
0.5 tab	0.5 tab	0.5 tab	0.5 tab	0.5 tab	0.5 tab	1 tab	**20 mg**	
0.5 tab	0.5 tab	0.5 tab	1 tab	0.5 tab	0.5 tab	1 tab	**22.5 mg**	
0.5 tab	1 tab	0.5 tab	1 tab	0.5 tab	0.5 tab	1 tab	**25 mg**	
0.5 tab	1 tab	0.5 tab	1 tab	0.5 tab	1 tab	1 tab	**27.5 mg**	
0.5 tab	1 tab	1 tab	1 tab	0.5 tab	1 tab	1 tab	**30 mg**	
0.5 tab	1 tab	1 tab	1 tab	1 tab	1 tab	1 tab	**32.5 mg**	
1 tab	1 tab	1 tab	1 tab	1 tab	1 tab	1 tab	**35 mg**	
1.5 tab	1 tab	1 tab	1 tab	1 tab	1 tab	1 tab	**37.5 mg**	
1.5 tab	1 tab	1 tab	1 tab	1.5 tab	1 tab	1 tab	**40 mg**	
1.5 tab	1 tab	1.5 tab	1 tab	1.5 tab	1 tab	1 tab	**42.5 mg**	
1.5 tab	1 tab	1.5 tab	1 tab	1.5 tab	1.5 tab	1 tab	**45 mg**	
1.5 tab	1.5 tab	1.5 tab	1 tab	1.5 tab	1.5 tab	1 tab	**47.5 mg**	
1.5 tab	1.5 tab	1.5 tab	1.5 tab	1.5 tab	1.5 tab	1 tab	**50 mg**	
1.5 tab	1.5 tab	1.5 tab	1.5 tab	1.5 tab	1.5 tab	1.5 tab	**52.5 mg**	

TWD: total weekly dose.

Adapted from: Horton JD, Bushwick BM. Warfarin therapy: Evolving strategies in anticoagulation. Am Fam Physician 1999; 59(3): 635-646. Review. Erratum in: Am Fam Physician 1999; 60: 1333. Am Fam Physician 2002; 65(2): 172.

TABLE A-9.2. Guide for Warfarin Monitoring and Dose Adjustment for Patients Requiring Less Than 17.5 mg/wk

TWD Using 3-, 2-, and 1-mg Tablets							
Day 1	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**TWD**
0	1 mg	1 mg	0	1 mg	0	1 mg	**4 mg**
0	1 mg	1 mg	0	1 mg	1 mg	1 mg	**5 mg**
0	1 mg	1 mg	1 mg	1 mg	1 mg	1 mg	**6 mg**
1 mg	1 mg	1 mg	1 mg	1 mg	1 mg	1 mg	**7 mg**
1 mg	1 mg	1 mg	2 mg	1 mg	1 mg	1 mg	**8 mg**
1 mg	2 mg	1 mg	2 mg	1 mg	1 mg	1 mg	**9 mg**
1 mg	2 mg	1 mg	2 mg	1 mg	2 mg	1 mg	**10 mg**
1 mg	2 mg	1 mg	2 mg	1 mg	2 mg	2 mg	**11 mg**
1 mg	2 mg	2 mg	2 mg	1 mg	2 mg	2 mg	**12 mg**
1 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	**13 mg**
2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	**14 mg**
3 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	**15 mg**
3 mg	2 mg	2 mg	2 mg	3 mg	2 mg	2 mg	**16 mg**
3 mg	2 mg	2 mg	2 mg	3 mg	2 mg	3 mg	**17 mg**

TWD: total weekly dose.

Adapted from: Horton JD, Bushwick BM. Warfarin therapy: Evolving strategies in anticoagulation. Am Fam Physician 1999; 59(3): 635-646. Review. Erratum in: Am Fam Physician 1999; 60: 1333. Am Fam Physician 2002; 65(2): 172.

APPENDIX 10. Warfarin 10 mg Initiation and Dosing Algorithm

ACCP 2012 suggests that in patients who are "sufficiently healthy to be treated as outpatients," warfarin be initiated at a dose of 10 mg/day for 2 days, followed by dosing based on INR measurements (Grade 2C).* This suggestion is based on a review of a case series of outpatients whose average age was 20 to 30 years younger than that of the average patient in the LTC setting. This initiation and dosing algorithm may, therefore, be inappropriate for frailer, older, more complex patients in this setting. A subset of relatively robust (usually short-stay) LTC patients, as well as many patients in assisted living settings, may, however, be appropriately treated with this algorithm.

* Holbrook A, Schulman S, Witt DM, et al. Evidence-based management of anticoagulant therapy: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012:141:e152S-e184S.

Day 3 INR	Days 3,4 Dose (mg)	Day 5 INR	Days 5, 6, 7 Dose (mg)
< 1.3	15, 15	< 2.0	15, 15, 15
		2.0 - 3.0	7.5, 5, 7.5
1.3 - 1.4	10, 10	3.1 - 3.5	0, 5, 5
		> 3.5	0, 0, 2.5
1.5 - 1.6	10, 5	< 2.0	7.5, 7.5, 7.5
		2.0 - 3.0	5, 5, 5
1.7 - 1.9	5, 5	3.1 - 3.5	2.5, 2.5, 2.5
		> 3.5	0, 2.5, 2.5
2.0 - 2.2	2.5, 2.5	< 2.0	5, 5, 5
		2.0 - 3.0	2.5, 5, 2.5
2.3 - 3.0	0, 2.5	3.1 - 3.5	0, 2.5, 0
		> 3.5	0, 0, 2.5
>3.0	0, 0	< 2.0	2.5, 2.5, 2.5
		2.0 - 3.0	2.5, 0, 2.5
		3.1 - 4.0	0, 2.5, 0
		> 4.0	0, 0, 2.5

- Day 1 = 1st day of warfarin
- All patients receive 10 mg Day 1 and Day 2
- INR in morning, drug given early evening

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