

Anticoagulants Review

01/25/2011

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Anticoagulants Review

FDA-Approved Indications

Drug	Manufacturer	DVT prophylaxis				DVT Treatment*
		Hip replacement	Knee replacement	Hip fracture surgery	Abdominal surgery	
Injectable						
dalteparin (Fragmin [®]) ¹	Eisai	X	-	-	X	-
enoxaparin (Lovenox [®]) ²	generic, Sanofi-Aventis	X	X	-	X	X (without PE in outpatient setting, with or without PE in inpatient setting)
fondaparinux (Arixtra [™]) ³	GlaxoSmithKline	X	X	X	X	X
tinzaparin (Innohep [®]) ⁴	Pharmion	-	-	-	-	X (inpatient setting only; with or without PE)
Oral						
dabigatran (Pradaxa [®]) ⁵	Boehringer Ingelheim	-	-	-	-	-
warfarin (Coumadin [®]) ⁶	generic, Bristol-Myers Squibb	X	X	X	X	X

*administered in conjunction with warfarin.

Other indications:

dalteparin (Fragmin)

- prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction (MI) when concurrently administered with aspirin
- DVT prophylaxis for immobile medical patients who are at risk for thromboembolic complications
- extended treatment of symptomatic venous thromboembolism (VTE) (proximal DVT and/or PE), to reduce the recurrence of VTE in patients with cancer

enoxaparin (Lovenox)

- for the prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction in conjunction with aspirin
- DVT prophylaxis to prevent thromboembolic complications in medical patients with severely restricted mobility during acute illness
- treatment of acute ST-segment elevation myocardial infarction (STEMI) managed medically or with subsequent percutaneous coronary intervention (PCI)

fondaparinux (Arixtra)

- treatment of acute PE when initial therapy is administered in the hospital and with warfarin

dabigatran (Pradaxa)

- stroke prophylaxis and systemic embolism prophylaxis in patients with non-valvular atrial fibrillation (AF)

warfarin (Coumadin)

- prophylaxis and/or treatment of the thromboembolic complications associated with atrial fibrillation (AF) and/or cardiac valve replacement
- reduce the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization after myocardial infarction
- prophylaxis and/or treatment of venous thrombosis and its extension, and pulmonary embolism (PE)

The focus of this review will be on the outpatient use of the injectable anticoagulants, which include the LMWHs and fondaparinux, and oral anticoagulants dabigatran and warfarin.

Overview

Venous thromboembolism (VTE) is a significant public health problem in the US. The disease manifests as deep vein thrombosis (DVT) and pulmonary embolism (PE) and is a major consequence of various surgical procedures and medical conditions. DVT occurs when a thrombus composed of cellular material bound together with fibrin strands forms in the deep venous portion of the extremities, most commonly the legs. Embolization of a thrombus results in PE if it lodges in the pulmonary artery or one of its branches and blocks pulmonary blood flow.^{7,8}

There are over 100,000 cases of PE annually in the United States. The National Institutes of Health (NIH) ranks PE as the third most common cause of death in hospitalized patients; if left untreated, approximately 30 percent of patients who develop PE will die within the first few hours of the event.⁹

Clinical risk factors for VTE include immobility or paralysis; trauma or surgery involving the lower extremities, pelvis, hips, or abdomen; malignancy; a history of VTE; obesity; any state leading to increased estrogen levels, including pregnancy and hormone replacement therapy; indwelling central venous catheters; cardiac dysfunction; inflammatory bowel disease; nephrotic syndrome; and acquired (e.g., cancer) or inherited hypercoagulability disorders. Generally, the risk of VTE increases with the number of risk factors present, major traumas, and age.^{10,11}

Due to the risk of morbidity and fatal PE associated with DVT, prophylaxis has become the standard of care for patients at high risk for thrombosis. Based on presence of the risk factors outlined above, the Eighth American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines published in 2008, recommend various regimens of parenteral and/or oral anticoagulants with or without mechanical devices such as graduated compression stockings and/or intermittent pneumatic compression devices.¹² For DVT prophylaxis, these guidelines add fondaparinux (Arixtra) as an alternative agent to subcutaneous (SC) low

molecular weight heparin (LMWH) and low-dose unfractionated heparin (UFH) for general medical patients, and certain patients undergoing general, vascular, thoracic, gynecologic, bariatric, or urologic surgery. In patients undergoing total hip replacement, knee replacement, or hip fracture surgery, DVT prophylaxis with LMWH, fondaparinux, or vitamin K antagonist [(VKA) e.g., warfarin] is recommended postoperatively for at least ten days and up to 35 days.

Treatment options for VTE consist of at least five days of either intravenous (IV) or SC UFH, SC LMWH or, fondaparinux, and until the international normalized ratio (INR) is therapeutic for at least 24 hours. Vitamin K antagonist (VKA) is given to overlap the parenteral anticoagulant therapy; it is initiated on the first treatment day rather than delayed initiation of VKA. For patients with VTE secondary to a transient (reversible) risk factor, treatment with VKA is recommended for three months. For patients with first episode of unprovoked DVT or PE, treatment with VKA is recommended for at least three months. The guidelines recommend VKA therapy be discontinued after three months with distal DVT and continued long-term for proximal DVT or PE in patients at low bleeding risk and good anticoagulant monitoring. For patients with unprovoked VTE who have a strong desire for less frequent INR monitoring, the guidelines recommend after the first three months of therapy with INR goal of 2 to 3 (conventional-intensity therapy) the INR goal be lowered to 1.5 to 1.9 (low-intensity therapy) with less frequent monitoring in lieu of discontinuing VKA therapy. The American College of Physicians (ACP) and The American Academy of Family Physicians (AAFP) in 2007 jointly recommend anticoagulation for three to six months for VTE secondary to transient risk factors and for more than 12 months for recurrent VTE. Although the appropriate duration of anticoagulation for idiopathic or recurrent VTE is not known, the ACP/AAFP guidelines state that there is evidence of substantial benefit for extended-duration therapy.¹³ For long-term treatment, SC anticoagulants are an alternative therapy for patients in whom oral anticoagulants cannot be used.¹⁴

The injectable agents in this review have different instructions for use and are not considered interchangeable, unit for unit. They differ in manufacturing process, molecular weight distribution, anti-Xa and anti-IIa activities, as well as units and dosage.¹⁵

For long-term anticoagulation, oral agents are preferred over parenteral drugs.¹⁶

Atrial fibrillation (AF) is a common arrhythmia in clinical practice with an estimated prevalence of 0.4 percent to one percent.¹⁷ The prevalence is higher in men than in women and with increasing age.¹⁸ Patients with AF can have a reduction in cardiac output resulting in pooling of blood in the heart, atrial thrombus formation and potential systemic embolization.¹⁹ Ischemic stroke is the most frequent clinical manifestation of AF associated embolization and averages five percent annually in patients with non-valvular AF.²⁰ In high-risk patients with AF, the annual stroke risk is six percent or greater, and patients strongly benefit from anticoagulation.²¹

Due to the high risk of future ischemic stroke, the 2008 ACCP guidelines recommend long-term anticoagulation with oral warfarin in patients with AF, including those with paroxysmal AF who have had a prior ischemic stroke, transient ischemic attack (TIA), or systemic embolism (Grade 1A).²² In patients with AF, including those with paroxysmal AF, who have two or more risk factors for future ischemic stroke (age>75 years, history of hypertension, diabetes mellitus, moderately or severely impaired left ventricular systolic function and/or heart failure), long-term anticoagulation with oral warfarin (Grade 1A) is also recommended. In patients with AF, including those with paroxysmal AF, with only one of the above risk factors, long-term antithrombotic therapy (Grade 1A), either as anticoagulation with oral warfarin (Grade 1A) or

aspirin, at a dose of 75–325 mg/day (Grade 1B), is recommended. In these patients at intermediate risk of ischemic stroke, warfarin rather than aspirin (Grade 2A) is recommended. In patients with AF, including those with paroxysmal AF, who are less than 75 years and have none of the other risk factors listed above, long-term therapy with aspirin at a dose of 75–325 mg/day (Grade 1B) is recommended due to their low risk of ischemic stroke. For AF patients, the target INR is 2.5 (range 2-3). The American College of Cardiology/American Heart Association/Heart Rhythm Society (ACCF/AHA/HRS) issued a focused update on treatment of AF and dabigatran (Pradaxa) in 2011.²³ Dabigatran is useful as an alternative to warfarin for the prevention of stroke and systemic thromboembolism in patients with paroxysmal to permanent AF and risk factors for stroke or systemic embolization who do not have a prosthetic heart valve or hemodynamically significant valve disease, severe renal failure (creatinine clearance <15 mL/min), or advanced liver disease (impaired baseline clotting function) (Class I; Level of Evidence B).²⁴

This focused update does not recommend routinely switching patients who are well maintained on warfarin to dabigatran. Selection of patients with AF and at least one additional risk factor for stroke who could benefit from dabigatran versus warfarin should include consideration for several clinical features including compliance with twice daily dosing, availability of a sustainable INR monitoring system, as well as other factors.

In patients with mechanical heart valves, warfarin therapy is recommended (Grade 1A). The target INR and range vary based on the type of replacement heart valve present.²⁵

Stroke is the third leading cause of death behind heart disease and cancer.²⁶ There is consensus in the guidelines that warfarin should be given to high-risk patients with atrial fibrillation; aspirin should be given to patients deemed to be at low risk. The 2011 American Heart Association/American Stroke Association (AHA/ASA) stroke primary prevention guidelines recommend warfarin (INR range 2 to 3) for all patients with nonvalvular atrial fibrillation at high-risk and many at moderate-risk for stroke who can receive it safely (Class I; Level of Evidence A).²⁷ Antiplatelet therapy with aspirin is recommended for low-risk and some moderate-risk AF patients based on estimated risk of bleeding if anticoagulated, access to high-quality anticoagulation monitoring, and patient preference (Class I; Level of Evidence A). However, warfarin continues to be underused, especially in very elderly patients with atrial fibrillation.^{28,29} The 2011 AHA/ASA guidelines for the prevention of stroke in patients with stroke or transient ischemic attack (TIA) recommend warfarin (INR 2-3) in patients with ischemic stroke or TIA with paroxysmal (intermittent) or permanent AF (Class I; Level of Evidence A).³⁰ Aspirin monotherapy is recommended for patients unable to take oral anticoagulants (Class I; Level of Evidence A). These guidelines do not provide recommendations for dabigatran (Pradaxa) due to the timing of FDA-approval.

Pharmacology

Unfractionated heparin and LMWH (dalteparin [Fragmin], enoxaparin [Lovenox], tinzaparin [Innohep]) are classified as indirect thrombin inhibitors because these agents exert anticoagulant action, in part, by binding to and potentiating the activity of antithrombin III (ATIII), a naturally occurring thrombin inhibitor. UFH exerts its anticoagulant effect by enhancing the capacity of ATIII to inactivate thrombin. LMWH also produces anticoagulant action through ATIII, however LMWH primarily inhibits clotting factor Xa rather than thrombin. Therefore, LMWH has less

effects on partial thromboplastin time (PTT), virtually eliminating the need for (and expense of) laboratory monitoring. LMWH exhibits more consistent bioavailability, resulting in less interpatient dose-response variation, and permitting standardized dosing. Another advantage of LMWH is the SC route of administration does not require an IV infusion pump. In addition, the incidence of thrombocytopenia appears to be lower with LMWH than with UFH.³¹

Fondaparinux (Arixtra) is a selective factor Xa inhibitor which binds to ATIII. By inhibiting factor Xa, thrombin generation and thrombus formation are inhibited without direct effects on thrombin. Also, fondaparinux does not bind significantly to platelet factor 4, a factor involved in immune-related heparin-induced thrombocytopenia (HIT).³²

Dabigatran etexilate (Pradaxa) is an oral prodrug of dabigatran. Dabigatran and its active metabolites (acyl glucuronides) are competitive, direct thrombin inhibitors. They inhibit both free and clot-bound thrombin. Dabigatran prevents thrombin-induced platelet aggregation and the development of a thrombus by preventing the thrombin-mediated conversion of fibrinogen to fibrin during the coagulation cascade.³³

Warfarin inhibits the synthesis of vitamin K-dependent coagulation factors II, VII, IX, and X and anticoagulant proteins C and S. Warfarin interferes with clotting factor synthesis by inhibition of the C1 subunit of the vitamin K epoxide reductase (VKORC1) enzyme complex, which reduces the regeneration of vitamin K1 epoxide. The degree of depression is dependent on the warfarin dose, and, to some extent, by the patient's VKORC1 genotype. The anticoagulant effects of warfarin are stereoselective; the S-isomer of warfarin is three to five times more potent than the R-isomer, but generally has a more rapid clearance. Therapeutic doses of warfarin decrease the total amount of active vitamin K dependent clotting factors made by the liver by 30 percent to 50 percent.³⁴

An anticoagulation effect generally occurs within 24 hours after administering warfarin. However, peak anticoagulant effects may be delayed 72 to 96 hours. The duration of action of a single dose of racemic warfarin is two to five days. Warfarin does not directly affect established thrombus and does not reverse ischemic tissue damage. Warfarin therapy prevents further extension of the formed clot and prevents secondary thromboembolic complications.³⁵

Pharmacokinetics^{36,37,38,39,40,41,42,43}

Drug	Bioavailability (%)	Half-life* (hrs)	Average molecular weight (daltons)	Anti-Xa : Anti-IIa activity	Peak Anti-Xa activity (hrs)
Injectable					
dalteparin (Fragmin) ⁴⁴	87	2-5	5,000	2-4 : 1	4
enoxaparin (Lovenox) ⁴⁵	~ 100	4.5-7	4,500	2.7-3.7 : 1	3-5
fondaparinux (Arixtra) ⁴⁶	~ 100	17-21	1,728	Anti-Xa only	3
tinzaparin (Innohep) ⁴⁷	86.7	3-4	5,500-7,500	1.5-2.8 : 1	4-5

Data presented for pharmacokinetics are for SC administration of all products.

*Delayed elimination of all the products may occur with severe liver or kidney insufficiency.

Pharmacokinetics (continued)

Drug	Bioavailability (%)	Half-life* (hrs)	Metabolism	Excretion
Oral				
dabigatran (Pradaxa) ⁴⁸	3-7	12-17	Esterase-catalyzed hydrolysis	Urine
warfarin (Coumadin) ⁴⁹	Completely absorbed; with peak concentration generally reached within first 4 hours.	20-60 (mean 40)	Hepatic-primarily via CYP2C9	Urine-92% primarily as metabolites

Contraindications/Warnings^{50,51,52,53,54,55}

All injectable agents in the class carry a black box warning regarding the risk of spinal/epidural hematomas when neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is performed in patients who are anticoagulated or scheduled to be anticoagulated with LMWHs, heparinoids, or fondaparinux (Arixtra) for prevention of thromboembolic complications. Epidural or spinal hematomas can result in long-term or permanent paralysis. Patients at highest risk are those with indwelling epidural catheters for administration of analgesia and patients concurrently on NSAIDs, platelet inhibitors, and other anticoagulants. Increased risk is also seen in traumatic or repeated epidural or spinal puncture. Frequent monitoring for signs and symptoms of neurologic impairment should be performed. The benefit and risks should be considered before neuraxial intervention in anticoagulated patients or patients to be anticoagulated for thromboprophylaxis.

LMWHs are contraindicated in patients with hypersensitivity to any LMWH, unfractionated heparin, or pork products.

Tinzaparin (Innohep) is not intended for intramuscular or intravenous use. Fondaparinux (Arixtra), enoxaparin (Lovenox), and dalteparin (Fragmin) should not be administered intramuscularly.

Fondaparinux and LMWH are contraindicated in patients with active major bleeding as well as patients with thrombocytopenia associated with a positive *in vitro* test for anti-platelet antibody in the presence of the respective agent. Thrombocytopenia of any degree should be monitored closely. If the platelet count falls below 100,000/mm³, therapy with agents in this class should be reevaluated and possibly discontinued.

LMWH should be used with extreme caution in patients with heparin-induced thrombocytopenia (HIT); this is considered a contraindication for tinzaparin.

Dalteparin is contraindicated in unstable angina, non-Q-wave MI, or acute venous thromboembolism in patients undergoing regional anesthesia.

Known hypersensitivity to benzyl alcohol is considered a contraindication only for tinzaparin and the multi-dose formulation of enoxaparin. Dalteparin multi-dose vials contain benzyl alcohol as a preservative.

For enoxaparin use associated with PCI, hemostasis at the puncture site should be obtained before sheath removal following percutaneous coronary revascularization.

Enoxaparin has not been adequately studied in pregnant women with mechanical prosthetic heart valves.

LMWHs and fondaparinux should be used cautiously in patients with renal insufficiency as the kidneys are the primary elimination route for the agents and such patients are at increased risk of major bleeding.

Tinzaparin should not be used in elderly patients with renal insufficiency due to increased risk of death.

Fondaparinux is contraindicated in patients with severe renal impairment (creatinine clearance less than 30 mL/min). Fondaparinux is also contraindicated in patients with body weight less than 50 kg when used for prophylaxis for abdominal surgery, hip fracture surgery, or hip or knee replacement surgery. In clinical trials, occurrence of major bleeding was doubled in patients with body weight less than 50 kg (5.4 percent) compared to heavier patients (2.1 percent). Fondaparinux is contraindicated in patients with bacterial endocarditis due to increased risk of bleeding.

LMWHs cannot be used interchangeably (unit for unit) with heparin or other LMWHs as they differ in manufacturing process, molecular weight distribution, anti-Xa and anti-IIa activities, units, and dosage.

Dabigatran is contraindicated in patients with active pathological bleeding or in patients with a history of a serious hypersensitivity reaction to dabigatran.

Dabigatran increases the risk of bleeding and can cause significant and, sometimes, fatal bleeding. Risk factors for bleeding include the use of drugs that increase the risk of bleeding in general (e.g., anti-platelet agents, heparin, fibrinolytic therapy, and chronic use of non-steroidal anti-inflammatory drugs [NSAIDs]) and labor and delivery. Promptly evaluate any signs or symptoms of blood loss (e.g., a drop in hemoglobin and/or hematocrit or hypotension). Discontinue dabigatran in patients with active pathological bleeding.

Warfarin carries a boxed warning for bleeding risk as it can cause major or fatal bleeding. Bleeding is more likely to occur during drug initiation and dose escalation (resulting in a higher INR). Risk factors for bleeding include high intensity anticoagulation (INR >4), age ≥65, highly variable INRs, history of gastrointestinal (GI) bleeding, hypertension, cerebrovascular disease, serious heart disease, anemia, malignancy, trauma, renal insufficiency, concomitant drugs, and long duration of warfarin therapy. Warfarin is contraindicated in pregnancy. Regular INR monitoring should be performed on all patients on warfarin. Many factors, alone or in combination, including changes in diet, medications, herbal medications, and genetic variations in the CYP2C9 enzymes involved in metabolic clearance of warfarin and Vitamin K epoxide reductase complex 1 (VKORC1) (which recycles vitamin K and is required for gamma carboxylation of vitamin K-dependent coagulation factors) enzymes may affect patient response to warfarin. Both endogenous and exogenous factors, alone or in combination, may be responsible for increased PT/INR response. Patients at high risk for bleeding may benefit from more frequent INR monitoring, careful dose adjustment to desired INR, and a shorter duration of

therapy. Patients should be educated about methods of reducing the risk of bleeding as well as immediately reporting signs and symptoms of bleeding to physicians.

Necrosis and/or gangrene of skin and other tissues have been reported with warfarin use. Hemorrhage and necrosis have, in some cases, resulted in death or permanent disability.

Systemic atheroemboli and cholesterol microemboli can present with a variety of signs and symptoms including purple toes syndrome, livedo reticularis, rash, gangrene, abrupt and intense pain in the leg, foot, or toes, foot ulcers, myalgia, penile gangrene, abdominal pain, flank or back pain, hematuria, renal insufficiency, hypertension, cerebral ischemia, spinal cord infarction, pancreatitis, symptoms simulating polyarteritis, or any other sequelae of vascular compromise due to embolic occlusion. The most commonly involved visceral organs are the kidneys, followed by the pancreas, spleen, and liver. Some cases have progressed to necrosis or death.

Warfarin should be used with caution in patients with heparin-induced thrombocytopenia (HIT) and deep venous thrombosis. Cases of venous limb ischemia, necrosis, and gangrene have been reported in patients with HIT and DVT when heparin treatment was discontinued and warfarin therapy was started or continued. In some patients sequelae have included amputation of the involved area and/or death.

Caution is recommended when warfarin is administered concomitantly with NSAIDs, including aspirin, to be certain that no change in warfarin dosage is needed. In addition to specific drug interactions that might affect PT/INR, NSAIDs (including aspirin) can inhibit platelet aggregation and lead to GI bleeding, peptic ulceration and/or perforation.

Treatment of each patient with warfarin is a highly individualized matter.

Drug Interactions^{56,57,58,59,60,61}

Due to the increased risk of bleeding, injectable anticoagulants should be used with caution with oral anticoagulants or platelet inhibitors, including aspirin, salicylates, NSAIDs, dipyridamole, dextran, ticlopidine, clopidogrel (Plavix[®]), and thrombolytics.

The concomitant use of dabigatran with P-gp inducers, such as rifampin, reduces exposure to dabigatran and should generally be avoided. P-gp inhibitors - ketoconazole, verapamil, amiodarone, quinidine, and clarithromycin - do not require dose adjustments. These results should not be extrapolated to other P-gp inhibitors.

Drug-drug interactions with warfarin can occur through pharmacodynamic or pharmacokinetic mechanisms. Pharmacodynamic mechanisms for drug interactions include synergism (impaired hemostasis, reduced clotting factor synthesis), competitive antagonism (vitamin K), and altered physiologic control loop for vitamin K metabolism (hereditary resistance). Pharmacokinetic mechanisms for drug interactions with warfarin are primarily enzyme induction, enzyme inhibition, and reduced plasma protein binding. Some drugs may interact by more than one mechanism.

Warfarin is stereoselectively metabolized by hepatic cytochrome P450 (CYP) isoenzymes to inactive, hydroxylated metabolites (predominant route) and by reductases to reduced metabolites (warfarin alcohols which have minimal anticoagulant activity). The CYP isoenzymes

involved in the metabolism of warfarin include 2C9, 2C19, 2C8, 2C18, 1A2, and 3A4. CYP2C9 is the major enzyme that metabolizes S-warfarin and modulates the *in vivo* activity of warfarin. CYP1A2 and CYP3A4 metabolize the R-isomer.

Genetic polymorphism of CYP2C9 may play a role in the interpatient variability of response to warfarin as well as predisposition to drug interactions. The variant alleles, CYP2C9*2 and CYP2C9*3, result in decreased hydroxylation of S-warfarin and decrease its clearance; the presence of > 1 of the CYP2C9 variant alleles further decreases clearance. For example, patients with CYP2C9 genotypes *1/*2 or *1/*3 have a clearance of 0.041 mL/min/kg versus 0.065 mL/kg/min in patients with CYP2C9 genotypes *1/*1. Additionally, patients with CYP2C9 genotypes *2/*2, *2/*3, or *3/*3 have a clearance of 0.02 mL/min/kg. In Caucasians, the frequency of the CYP2C9*2 variant is 8-20 percent, while the frequency of the CYP2C9*3 variant is 6-10 percent. The presence of CYP2C9*2 and *3 variant alleles in Blacks and Asians are much lower (0-4 percent); other CYP2C9 alleles that may decrease warfarin metabolism occur at lower frequencies in all races. Poor CYP2C9 metabolizers are more dependent on the metabolism of S-warfarin by the CYP3A4 pathway. Drugs that affect any of the enzymes involved in the metabolism of warfarin may alter the anticoagulation response. As a result, drugs that preferentially induce S-warfarin metabolism impair coagulation to a greater degree than those that induce the metabolism of R-warfarin.

Exogenous administration of vitamin K, such as enteral feedings, certain multivitamins, and many foods, can decrease or reverse the activity of warfarin.⁶² Patient response to warfarin usually returns after stopping the vitamin K-containing agent. Foods that contain large to moderate amounts of vitamin K include green tea, brussel sprouts, kale, asparagus, avocado, broccoli, cabbage, cauliflower, collard greens, lettuce, liver, soy products (including soy milk, soybeans or soybean oil), lentils, peas, mustard greens, turnip greens, parsley, green scallions, and spinach. Medical products that contain soybean oil such as intravenous lipid emulsions or propofol, can decrease warfarin anticoagulation. Patients should avoid large amounts/frequent servings of vitamin K-containing foods or maintain a constant vitamin K diet.

Adverse Effects

Drug	Major bleeding	Thrombocytopenia	Injection site reactions
Injectable			
dalteparin (Fragmin) ⁶³	0 - 4.6	<1	2-12
enoxaparin (Lovenox) ⁶⁴	< 1-4	0.1-1.3	Reported
fondaparinux (Arixtra) ⁶⁵	2.2-3.4	0.04-3	Reported
tinzaparin (Innohep) ⁶⁶ Treatment	0.8	0.13-1	16

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not comparative. All adverse effects are reported for prophylaxis except tinzaparin (Innohep) which is only approved for treatment of VTE.

Direct comparison of bleeding risks among the injectable anticoagulants is difficult due to different definitions of bleeding in various clinical studies.

Most common adverse effects with dabigatran in clinical trials were gastritis-like symptoms (>15 percent) and bleeding. Gastrointestinal complaints included dyspepsia, nausea, upper abdominal pain, gastrointestinal hemorrhage, and diarrhea; specific percentages were not reported. Serious bleeding including intracranial hemorrhage, life threatening bleeding, and major bleeds were reported in dabigatran and warfarin treatment groups. The percentage of any bleed for dabigatran and warfarin was 16.6 percent and 18.4 percent, respectively. There was a higher rate of major gastrointestinal bleeds in patients receiving dabigatran 150 mg than in patients receiving warfarin (1.6 percent versus 1.1 percent, respectively, with a hazard ratio versus warfarin of 1.5, 95% CI, 1.2 to 1.9), and a higher rate of any gastrointestinal bleeds (6.1 percent versus 4 percent, respectively).

Adverse events with warfarin include fatal or nonfatal hemorrhage, including major bleeding from any tissue or organ. The incidence of major bleeding in the atrial fibrillation trials ranged from 0.6 percent to 2.7 percent. Hemorrhagic complications may present as paralysis; paresthesia; headache, chest, abdomen, joint, muscle or other pain; dizziness; shortness of breath, difficult breathing or swallowing; unexplained swelling; weakness; hypotension; or unexplained shock. Bleeding can occur when the PT/INR is within the therapeutic range. Necrosis of skin and other tissues has been reported.

There is no antidote for dabigatran. Fresh frozen plasma and red blood cells can be used for management of bleeding. Phytonadione (Vitamin K1) is the antidote for warfarin. Protamine is used as an antidote for LMWH and UFH.

Special Populations^{67,68,69,70,71,72}

Pediatrics

Safety and effectiveness of LMWH and fondaparinux (Arixtra) in pediatric patients have not been established. Since risk for bleeding during treatment with fondaparinux is increased in adults who weigh less than 50 kg, bleeding may be a particular safety concern for use of fondaparinux in the pediatric population.

The 2008 ACCP guidelines state that despite their unproven efficacy, LMWHs have rapidly become the anticoagulant of choice in many pediatric patients, both for primary prophylaxis and treatment of thromboembolism.⁷³

Potential advantages of LMWH in children include predictable pharmacokinetics requiring minimal monitoring, which is critically important in pediatric patients with poor or nonexistent venous access; SC administration; lack of drug or food interactions, such as those that exist for vitamin K antagonist (VKA); reduced risk of HIT; and probable reduced risk of osteoporosis with long-term use, which occurs with UFH. The guidelines point out that although they use the term LMWH and present dosing schedules for a number of different LMWHs, the majority of all clinical data with respect to LMWH use in children is from studies that used enoxaparin.⁷⁴

The 2008 ACCP guidelines recommend anticoagulant therapy with either UFH or LMWH in children with DVT. Initial treatment with UFH or LMWH should be for at least five to ten days. If warfarin will be subsequently prescribed, oral warfarin should be initiated as early as day one and discontinue LMWH or UFH on day six or later than day six if the INR has not exceeded 2. After the initial five to ten day treatment period, the guidelines suggest LMWH rather than warfarin therapy if therapeutic levels are difficult to maintain on warfarin therapy or if warfarin therapy is challenging for the child and family (Grade 2C). Warfarin or alternatively LMWH are recommended for children with idiopathic thromboembolism as in children with secondary thrombosis (in whom the risk factor has resolved) for at least six months and at least three months, respectively (Grade 2C).

A study with 27 children evaluated enoxaparin for the treatment of DVT.⁷⁵ Neonates through adolescents were included. Doses of enoxaparin administered were 1.5 mg/kg twice daily for neonates and infants, and 1 mg/kg twice daily for children. Mean duration of treatment was 16.5 days followed by a mean prophylaxis period of 9.8 months. Anti-Xa activity treatment goals were achieved in 85 percent of patients. Re-thrombosis and HIT were not observed in any patient in the study.

Children over three months old with DVT were treated with enoxaparin to a target four-hour anti-factor Xa activity between 0.5-0.8 IU/mL.⁷⁶ In the open-label trial of 80 children, the patients were stratified to receive once daily or twice daily doses of enoxaparin for a median duration of five months. Endpoints were post-thrombotic syndrome, re-thrombosis, bleeding, and therapy-related death. No significant differences were observed between treatment groups. No bleeding or therapy-related deaths occurred. The median follow-up was 24 months.

Safety and effectiveness of dabigatran or warfarin in pediatric patients have not been established. However, warfarin has been used in pediatric patients for the prevention and treatment of thromboembolic events. Difficulty achieving and maintaining therapeutic PT/INR ranges in the pediatric patient has been reported; more frequent PT/INR monitoring are recommended due to potential varying warfarin requirements.⁷⁷

Pregnancy

All four injectable agents in this class are Pregnancy Category B.

Dabigatran is Pregnancy Category C. Warfarin is Pregnancy Category X.

All patients receiving anticoagulants, including pregnant women, are at risk for bleeding. Pregnant women receiving enoxaparin should be carefully monitored for evidence of bleeding or excessive anticoagulation. Hemorrhage can occur at any site and may lead to death of mother and/or fetus.

Pregnant women have a five-fold increased risk of an event compared with non-pregnant women. According to the 2007 ACP/AAFP guidelines, there is insufficient evidence to make specific recommendations for types of anticoagulation management of VTE in pregnancy.⁷⁸

LMWH or UFH are recommended by the 2008 ACCP for treatment and/or prophylaxis in pregnant women who have an increased risk for DVT and/or PE.⁷⁹ In contrast to VKA, LMWH and UFH do not cross the placenta and do not have the potential to cause fetal bleeding and/or

malformations.^{80,81} Although the efficacy of LMWH and UFH for this indication has not been verified by randomized, controlled trials, extrapolation of data from non-pregnant patients, along with the relative safety in this patient population, support the recommendation. Because of the lack of data, the ACCP guidelines make no distinction among enoxaparin (Lovenox), dalteparin (Fragmin), or tinzaparin (Innohep) for this use. More randomized, well-controlled trials are needed to evaluate use of LMWH as prophylaxis in pregnancy and the early post-natal period, according to a systematic review.⁸² There are only limited data available regarding the safety of fondaparinux (Arixtra) during pregnancy. Therefore, the 2008 ACCP guidelines recommend against its general use in pregnancy.⁸³

A substudy of the ongoing Thrombophilia in Pregnancy Prophylaxis study (TIPPS) determined long term prophylactic dalteparin (Fragmin) in pregnancy did not result in a significant decrease in maternal bone mineral density.⁸⁴ Based on data from 62 patients, there was no difference in mean BMD between the patients receiving dalteparin or the control group. TIPPS is expected to conclude in 2011.⁸⁵

The Efficacy of Thromboprophylaxis as an Intervention during Gravidity (ETHIG) was a prospective trial of 810 pregnant women assigned to one of three management strategies according to predefined VTE risk factors.⁸⁶ The low risk (group I) received dalteparin 50-100 IU/kg body weight for 14 days postpartum. The high (group II) or very high risk (group III) received dalteparin 50-100 IU/kg/day and 100-200 IU/kg/day, respectively) from enrollment until six weeks postpartum. Symptomatic VTE occurred in 5/810 women (0.6 percent, 95% CI, 0.2-1.5) (group I, 0 of 225; II, 3/469; III, 2/116). Serious bleeding occurred in three percent (95% CI, 1.9-4.4); 1.1 percent (95% CI, 0.5-2.2) was possibly dalteparin-related. There was no evidence of heparin-induced thrombocytopenia (HIT) and one case of osteoporosis. Risk-stratified heparin prophylaxis was associated with a low incidence of symptomatic VTE and few clinically important adverse events.

Renal Impairment

The risk of bleeding with LMWH increases with creatinine clearance of less than 30 mL/min.⁸⁷ The dose and/or frequency of administration of enoxaparin (Lovenox) should be reduced to daily in patients with severe renal insufficiency. Dalteparin (Fragmin) and tinzaparin (Innohep) should be used with caution in patients with renal insufficiency. Fondaparinux (Arixtra) is contraindicated in patients with severe renal insufficiency (creatinine clearance < 30 mL/min).

No dose adjustment of dabigatran is recommended in patients with mild or moderate renal impairment. Reduce the dose of dabigatran in patients with severe renal impairment (creatinine clearance [CrCl] 15-30 mL/min) to 75 mg twice daily. Dosing recommendations for patients with CrCl <15 mL/min or on dialysis cannot be provided.

Patients with renal failure have an increased risk of bleeding complications, so monitor patients with moderate renal insufficiency who are taking warfarin very closely.

Hepatic Impairment

Patients with hepatic impairment may be particularly vulnerable to bleeding during fondaparinux (Arixtra) therapy. Although not evaluated, enoxaparin (Lovenox) should be used with caution in patients with hepatic impairment.

Anticoagulants

Patients taking dabigatran with mild to moderate hepatic impairment (Child Pugh B) demonstrated greater variability in pharmacokinetic parameters; no dosage adjustment information is provided for dabigatran.

Anticoagulant response may be enhanced in obstructive jaundice, hepatitis, and cirrhosis. Monitor warfarin patients with moderate hepatic insufficiency more cautiously.

Geriatrics

In the major dabigatran clinical trial (RE-LY), 82 percent of patients were older than 65 years of age, while 40 percent were 75 years and over. The risk of stroke and bleeding increases with age, but the risk-benefit profile is favorable in all age groups.

Patients aged 60 years or older have a greater than expected PT/INR response to warfarin. Therefore, a lower dose of warfarin is usually required to produce a therapeutic level of anticoagulation, with increasing age.

Race

Asian patients may require lower initiation and maintenance doses of warfarin. Refer to Drug Interactions section for further information.

Pharmacogenomics

When available, the patient's CYP2C9 and VKORC1 genotype information can assist in selection of the starting warfarin dose. In all patients, subsequent dosage adjustments must be made based on the results of INR determinations.

Dosages

Drug	DVT prophylaxis					DVT treatment (outpatient)*
	Hip replacement**	Knee replacement **	Hip fracture surgery**	Abdominal surgery	Medical	
Injectable						
dalteparin (Fragmin) ⁸⁸	5,000 units once daily for 5 to 10 days	--	--	2,500 to 5,000 units once daily for 5 to 10 days	5,000 units once daily for 12 to 14 days	--
enoxaparin (Lovenox) ⁸⁹	30 mg every 12 hours OR 40 mg once daily for 7 to 10 days	30 mg every 12 hours for 7 to 10 days	--	40 mg once daily for 7 to 10 days	40 mg once daily for 6 to 11 days	1 mg/kg every 12 hours
fondaparinux (Arixtra) ⁹⁰	2.5 mg daily for 5 to 9 days	2.5 mg daily for 5 to 9 days	2.5 mg daily for 5 to 9 days and up to 24 days	2.5 mg daily for 5 to 9 days	--	Based on patient's weight: <50 kg: 5 mg daily 50-100 kg: 7.5 mg daily >100 kg: 10 mg daily
tinzaparin (Innohep) ⁹¹	--	--	--	--	--	175 units/kg once daily

All dosages are given subcutaneously.

*Given for at least five days (at least six days for tinzaparin) and until a therapeutic oral anticoagulant effect is established (INR 2 to 3).

**The ACCP Chest guidelines recommend at least ten days and an extended thromboprophylaxis of up to 35 days after surgery in patients undergoing total hip replacement, hip fracture, or knee replacement surgery.⁹²

Renal impairment: Dalteparin (Fragmin) and tinzaparin (Innohep) should be used with caution in patients with renal insufficiency, although specific dosage adjustment guidelines are not available.

Recently the Innohep in Renal Insufficiency Study (IRIS) compared tinzaparin (Innohep) and UFH in the initial treatment of DVT and/or PE in elderly patients with renal insufficiency (patients ≥ 70 years with estimated CrCl ≤ 30 mL/min or patients ≥ 75 years with estimated CrCl ≤ 60 mL/min). Study treatment was continued for at least five days and until INR was therapeutic. Oral anticoagulant was overlapped and continued for 90 days after start of treatment. Mortality rate in the tinzaparin and UFH groups were 11.2 and 6.3 percent, respectively. Due to this increased risk of death with tinzaparin, alternatives to tinzaparin should be considered when treating all elderly patients with renal insufficiency for DVT with or without PE.⁹³

The 2008 ACCP guidelines suggest that if LMWHs are used in patients with severe renal insufficiency, 50 percent of the recommended LMWH dose be used (Grade 2C).⁹⁴

Extended treatment in patients with cancer and symptomatic venous thromboembolism:

Dalteparin (Fragmin): In these patients, dalteparin therapy begins with the initial VTE treatment and continues for six months. For the first 30 days, dalteparin 200 IU/kg SC is administered once daily. Dosage should not exceed 18,000 IU. For months two through six, dalteparin is given as 150 IU/kg once daily. The daily dose of dalteparin should be reduced by 2,500 IU for patients who have reduced platelet counts (50,000 to 100,000/mm³) until the platelet count exceeds 100,000/mm³. Patients with platelet counts less than 50,000/mm³ should not receive dalteparin until platelet count exceeds 50,000/mm³. Dose reductions are also necessary for patients with impaired renal function.

Oral

Dabigatran is administered to patients with CrCl >30 mL/min as 150 mg orally twice daily. For patients with renal impairment, defined as CrCl 15-30 mL/min, dabigatran dose should be reduced to 75 mg orally twice daily. Dabigatran capsules should not be broken, chewed, or opened before administration as the oral bioavailability increases by 75 percent when the pellets are administered without the capsule shell. Temporarily discontinue dabigatran before invasive or surgical procedures when possible; restart promptly.

Dosing instructions for converting patients from warfarin to/from dabigatran appear in the prescribing information. To switch from warfarin to dabigatran, discontinue warfarin and start dabigatran when the international normalized ratio (INR) is below 2. When switching from dabigatran to warfarin, adjust the starting time of warfarin based on CrCl as follows: for CrCl >50 mL/min, start warfarin three days before discontinuing dabigatran. For CrCl 31-50 mL/min, start warfarin two days before discontinuing dabigatran. For CrCl 15-30 mL/min, start warfarin one day before discontinuing dabigatran. For CrCl <15 mL/min, no recommendations can be made. Because dabigatran can contribute to an elevated INR, the INR will better reflect warfarin's effect after dabigatran has been stopped for at least two days.

Warfarin dosing should be individualized by monitoring the PT/INR. Some of the factors influencing warfarin dose variability include clinical (age, race, body weight, sex, concomitant medications, and comorbidities) and genetic (CYP2C9 and VKORC1 genotypes).

Warfarin loading doses are not recommended due to increase in hemorrhagic and other complications. In addition, the loading dose does not offer more rapid protection against clot formation. If the patient's CYP2C9 and VKORC1 genotypes are unknown, a typical initial dose is 2 to 5 mg per day. PT/INR response determines maintenance doses and intervals. If large daily doses of warfarin are required to maintain a patient's PT/INR within a normal therapeutic range, acquired or inherited warfarin resistance (although rare) should be suspected. Lower initiation and maintenance doses should be considered for elderly and debilitated patients.

Duration of therapy should be individualized and followed according to current treatment guidelines. An INR of greater than 4 appears to provide no additional therapeutic benefit in most patients and is associated with a higher risk of bleeding.

PT/INR should be done daily after the initial dose of warfarin and results stabilize in the therapeutic range. Intervals between subsequent PT/INR should be based upon the physician's judgment of the patient's reliability and response to warfarin in order to maintain therapeutic range. Acceptable intervals for PT/INR determinations are within the range of one to four weeks once a stable dosage has been determined. Studies suggest that patients in usual care monitoring are in therapeutic range only 33 percent to 64 percent of the time. Time in therapeutic range is higher at 56 percent to 93 percent in patients managed by anticoagulation clinics, among self-testing/self-monitoring patients, and in patients managed with the help of computer programs.⁹⁵

Availability

Drug	Prefilled syringes	Vials
Injectable		
dalteparin (Fragmin)	2,500, 5,000, 7,500, 10,000, 12,500, 15,000 or 18,000 units	10,000 units/mL in 9.5 mL MDV 25,000 units/mL in 3.8 mL MDV
enoxaparin (Lovenox)	30, 40, 60, 80, 100, 120, 150 mg	100 mg/mL in 3 mL MDV (brand only)
fondaparinux (Arixtra)	2.5, 5, 7.5, 10 mg	-
tinzaparin (Innohep)	-	20,000 units/mL in 2 mL MDV

MDV = multiple-dose vial

Drug	Availability
Oral	
dabigatran (Pradaxa)	75 mg, 150 mg capsules
warfarin (Coumadin)	1, 2, 2.5, 3, 4, 5, 6, 7.5, 10 mg tablets

Dabigatran 110 mg strength was studied but did not receive FDA-approval.

Dabigatran capsules should not be chewed or broken open as this increases bioavailability by 75 percent. Open bottles of dabigatran have to be used within 30 days of being opened.

Injectable warfarin (brand Coumadin only) is also available as a 5 mg/single-use vial. It offers an alternate route of administration for patients who cannot receive oral medication. The intravenous (IV) dosages would be the same as those for oral warfarin (Coumadin).

Clinical Trials

Search Strategy

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class for the FDA-

approved indications used in the outpatient setting. Randomized, controlled trials comparing agents for either the treatment or prophylaxis of DVT in the outpatient setting or non-valvular atrial fibrillation are considered the most relevant in this category. Comparative trials are the most important, but when comparative trials were unavailable, placebo-controlled trials were considered relevant. In comparisons with UFH, studies utilizing weight-based dosing of UFH with adjustments according to laboratory parameters were considered most useful. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

DVT

Prophylaxis

dalteparin (Fragmin) versus fondaparinux (Arixtra)

In the Pentasaccharide General Surgery (PEGASUS) study, 2,297 surgical patients were randomized in double-blind fashion to receive either fondaparinux 2.5 mg or dalteparin 5,000 units SC daily.⁹⁶ Fondaparinux was initiated six hours after high risk abdominal surgery. Dalteparin was initiated as 2,500 units given two hours preoperatively and repeated 12 hours later. There was no difference between the two treatment arms in occurrence of venous thromboembolism up to post-operative day 10 (4.6 versus 6.1 percent for fondaparinux and dalteparin, respectively), a relative risk reduction of 24.6 percent [95% Confidence Interval (CI), -9 to 47.9, $p=0.144$]; this met the pre-determined criterion for non-inferiority of fondaparinux. No difference was detected in the primary safety outcome, major bleeding, during the initial treatment period. The rate of major bleeding was 3.4 percent in the fondaparinux group and 2.4 percent in the dalteparin group.

dalteparin (Fragmin) versus warfarin

In the double-blind, North American Fragmin trial, 1,472 patients were randomized to dalteparin given once daily immediately or early after surgery or post-operative warfarin for DVT prophylaxis in patients undergoing hip arthroplasty.⁹⁷ Venograms were performed five days after surgery. The dalteparin group had 10.7 percent positive for any DVT whereas the warfarin group had 24 percent positive for any DVT ($p<0.001$). Proximal DVTs were identified in 0.8 percent of dalteparin patients and three percent of the warfarin patients ($p=0.03$ and $p=0.04$). Serious bleeding was similar in both groups. Pre-operative dalteparin patients experienced more major surgical site bleeding than did the warfarin patients ($p=0.01$). When evaluating extended out-of-hospital use for up to 35 days with dalteparin or placebo, new proximal DVT rates were 0.7 to 1.3 percent of dalteparin patients and 4.8 percent for the inpatient warfarin group.⁹⁸ Overall, the cumulative incidence of all DVT was 17.2 to 22.2 percent with dalteparin and 36.7 percent with in-hospital warfarin/out-of-hospital placebo group. Cumulative proximal DVT rates were 2 to 3.1

percent for dalteparin and 9.2 percent for the warfarin/placebo groups. No major bleeding occurred during the extended prophylaxis time period.

A multicenter, randomized, open-label trial compared the efficacy of dalteparin with a coumarin derivative to prevent recurrent thrombosis in 672 patients with cancer.⁹⁹ Patients with cancer who had acute, symptomatic proximal DVT, PE or both were randomized to dalteparin 200 IU/kg daily SC for five to seven days and an oral anticoagulant, warfarin or acenocoumarol, for six months (INR target 2.5) or dalteparin alone given as 200 IU/kg daily for one month followed by 150 IU/kg for five months. Recurrent venous thromboembolism was reported in 8 percent and 15.8 percent of patients receiving dalteparin and oral anticoagulant, respectively over the six-month study period (hazard ratio=0.47, p=0.002). The probability of recurrent thromboembolism at six months was 17 percent in the dalteparin plus oral anticoagulant group and 9 percent in the dalteparin only group. Rates of major bleeding for dalteparin plus oral anticoagulant (six percent) and dalteparin alone (four percent) were similar (p=0.27). Mortality rates at six months were 39 percent in the dalteparin only group and 41 percent in the dalteparin plus oral anticoagulant group (p=0.53).

enoxaparin (Lovenox) versus fondaparinux (Arixtra)

A multicenter, randomized, double-blind trial compared enoxaparin and fondaparinux in patients undergoing elective knee surgery.¹⁰⁰ Patients (n=1,049) were randomized to receive enoxaparin 30 mg SC twice daily or fondaparinux 2.5 mg SC once daily. Both drugs were started postoperatively. The primary efficacy endpoint, incidence rate of VTE, was determined by day 11. Diagnosis of VTE was completed by bilateral leg venography assessing for DVT, and for PE, diagnosis was made by lung scan indicating a high probability of pulmonary embolism, by pulmonary angiography, by helical computed tomography, or at autopsy. The primary safety outcome was major bleeding. Incidence of VTE by day 11 was significantly lower in the fondaparinux group (12.5 percent) than the enoxaparin group (27.8 percent; p<0.001). The rate of symptomatic venous thrombosis was similar between the groups. More major bleeding was observed in the fondaparinux group (p=0.006).

In a multicenter, randomized, double-blind trial, enoxaparin 40 mg and fondaparinux 2.5 mg, each given SC once daily, were compared in 1,711 patients undergoing hip fracture surgery.¹⁰¹ Enoxaparin therapy was initiated pre-operatively whereas fondaparinux was initiated post-operatively; treatment continued for at least five days in both groups. The primary efficacy endpoint was the rate of VTE up to day 11; the primary safety outcomes were major bleeding and all-cause mortality through six weeks. In the study, the incidence of VTE was significantly lower in the fondaparinux group (8.3 percent) than the enoxaparin group (19.1 percent; p<0.001). Symptomatic venous thrombosis was similar between the groups. There were no significant differences between the two groups in the incidence of death or rate of clinically relevant bleeding.

In the double-blind European Pentasaccharide Hip Elective Surgery Study (EPHESUS), 2,309 consecutive adult patients undergoing elective hip replacement surgery were randomly assigned in a double-blind manner to fondaparinux 2.5 mg SC daily, starting postoperatively, or enoxaparin 40 mg SC daily, starting preoperatively.¹⁰² The primary efficacy outcome was VTE up to day 11; primary safety outcomes were bleeding and death through six weeks. Primary efficacy analysis was performed in 908 fondaparinux patients and 919 enoxaparin patients. By day 11, four percent of fondaparinux patients experienced VTE whereas nine percent of

enoxaparin patients had positive findings for VTE (55.9 percent relative risk reduction, $p < 0.0001$). The two groups did not differ significantly in incidence of death or rate of clinically relevant bleeding.

In the similarly designed PENTATHLON 2000 study, 2,275 consecutive adult patients who were undergoing elective hip replacement surgery were randomized in a double-blind manner to receive either fondaparinux 2.5 mg SC once daily or enoxaparin 30 mg SC twice daily.¹⁰³ The primary efficacy of the presence of VTE was assessed to day 11 in 1,584 patients. Venous thromboembolism was reported in six percent of patients on fondaparinux and eight percent of patients receiving enoxaparin ($p = \text{NS}$). The two groups did not differ in the number of patients who died or in the number who had clinically relevant bleeding.

enoxaparin (Lovenox) versus tinzaparin (Innohep)

A multicenter trial randomly assigned 499 consecutive patients undergoing total hip replacement to either tinzaparin 4,500 units or enoxaparin 40 mg SC daily for the prevention of DVT.¹⁰⁴ In the blinded study, LMWH was given 12 hours before and 12 hours after surgery, then daily. A total of 440 patients underwent a venogram. At 12 to 14 days after surgery, the overall rate of DVT was 21.7 percent in the tinzaparin group and 20.1 percent in the enoxaparin group ($p = \text{NS}$). The rate of proximal DVT was similar in both groups, occurring in 10.5 percent of the enoxaparin group and 9.5 percent of the tinzaparin group ($p = \text{NS}$). No major bleeding was observed.

Treatment (Outpatient)

enoxaparin (Lovenox) versus fondaparinux (Arixtra)

MATISSE DVT trial was a multicenter, double-blind study including 2,205 patients with acute symptomatic DVT. The patients were randomized to receive enoxaparin 1 mg/kg SC twice daily or fondaparinux 7.5 mg SC once daily for at least five days and until the INR was above 2.¹⁰⁵ Vitamin K antagonist therapy was initiated within 72 hours of either randomized therapy. Doses for fondaparinux were adjusted for patients weighing less than 50 kg (fondaparinux 5 mg SC daily) and more than 100 kg (fondaparinux 10 mg SC daily). The rates of recurrent thromboembolic events (primary outcome) were similar in the enoxaparin and fondaparinux groups (4.1 and 3.9 percent, respectively; $p = \text{NS}$). Major bleeding occurred in 1.2 percent of patients receiving enoxaparin and 1.1 percent of patients receiving fondaparinux ($p = \text{NS}$).

tinzaparin (Innohep) versus UFH

A trial conducted by the American-Canadian Thrombosis Study Group compared tinzaparin with IV UFH for the treatment of PE.¹⁰⁶ In the double-blind trial, 200 patients with high-probability lung scans were randomized to once daily SC tinzaparin or to adjusted-dose IV UFH. New VTE was documented in none of the patients who received tinzaparin compared with 6.8 percent of patients who received UFH ($p = 0.01$). Major bleeding occurred in one patient (one percent) on tinzaparin and two patients (1.9 percent) on UFH. The results of the study support that tinzaparin is at least as effective as UFH for preventing recurrent VTE in patients with PE.

Nonvalvular AF

Warfarin (Coumadin) was approved in the US in 1954.¹⁰⁷ It has established itself as a highly effective strategy for the treatment of VTE and is often used with UFH, LMWH, or

fondaparinux.¹⁰⁸ Adjusted-dose warfarin has also demonstrated efficacy for the long-term prevention of VTE recurrence in most patients.^{109,110} Adjusted-dose warfarin has consistently established itself in randomized trials for prevention of stroke in younger (averaging about 70 years old) patients with non-valvular atrial fibrillation.^{111,112} Adjusted-dose warfarin has shown superiority to aspirin by demonstrating 54 percent relative risk reduction of stroke in older non-valvular atrial fibrillation patients (≥ 75 years) with similar bleeding rates.¹¹³ Dabigatran is the first oral anticoagulant to receive FDA-approval which, based on the RE-Ly trial, has demonstrated similar to superior efficacy over warfarin for reduction of stroke and thromboembolism risk in patients with non-valvular atrial fibrillation.

Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial: Dabigatran and warfarin were compared in a randomized, blinded, non-inferiority trial with 18,113 patients with atrial fibrillation and a risk for stroke over two years.¹¹⁴ Risk factors considered in the trial included previous stroke or transient ischemic attack, a left ventricular ejection fraction of less than 40 percent, New York Heart Association class II or higher heart-failure symptoms within six months before screening, and an age of at least 75 years or an age of 65 to 74 years plus diabetes mellitus, hypertension, or coronary artery disease. Patients were randomized to dabigatran 110 mg or 150 mg twice daily (blinded or unblinded) or adjusted-dose warfarin (INR target 2 to 3). In the warfarin group, the mean percentage of the study period during which the INR was within the therapeutic range was 64 percent. The rate of stroke or systemic embolism, the primary outcome measure, was 1.69 percent in the warfarin group and 1.53 percent for dabigatran 110 mg group (relative risk: 0.91; 95% confidence interval [CI], 0.74 to 1.11; $p < 0.001$ for non-inferiority) and 1.11 percent for dabigatran 150 mg group (relative risk, 0.66; 95% CI, 0.53 to 0.82; $p < 0.001$ for superiority). Both doses of dabigatran were non-inferior to warfarin ($p < 0.001$). Rates of major bleeding were 3.36 percent, 2.71 percent, and 3.11 percent for the warfarin, dabigatran 110 mg group ($p = 0.003$), and dabigatran 150 mg group ($p = 0.31$ versus warfarin), respectively. The rates of hemorrhagic stroke were 0.38 percent per year in the warfarin group, 0.12 percent per year with dabigatran 110 mg ($p < 0.001$) and 0.1 percent per year with dabigatran 150 mg ($p < 0.001$). Mortality rates were 4.13 percent per year in the warfarin group, 3.75 percent per year with dabigatran 110 mg ($p = 0.13$), and 3.64 percent per year with dabigatran 150 mg ($p = 0.051$). Both doses of dabigatran had a small but significantly higher rate of myocardial infarction (MI) versus warfarin, 0.72 percent per year for dabigatran 110 mg, 0.74 percent per year for dabigatran 150 mg, and 0.53 percent per year for warfarin. However, after study reevaluation for adverse event underreporting, the MI rate was not significant.¹¹⁵ Dyspepsia was more common in the dabigatran 110 mg (11.8 percent) and 150 mg (11.3 percent) groups compared to the warfarin group (5.8 percent; both $p < 0.001$).

Previous warfarin exposure does not appear to influence the benefits of dabigatran.¹¹⁶ An analysis of the RE-LY study found that regardless of the individual center's quality of INR control, dabigatran maintained its benefits over warfarin.¹¹⁷ However, these advantages were greater at centers with poor INR control. According to a pre-defined analysis, most effects of both doses of dabigatran versus warfarin were consistent in the subgroup of patients with previous stroke or transient ischemic attack (TIA).^{118,119}

Meta-analysis

Two different meta-analyses evaluated the randomized, controlled trials of LMWH versus UFH in the treatment of acute DVT.^{120,121} The LMWHs were shown to reduce mortality rates after acute DVT and appeared as safe as UFH and provide similar efficacy. Initial therapy of PE with LMWH also appears as effective as UFH.

A Cochrane database systemic review evaluated the safety and efficacy of three types of anticoagulants: LMWH, UFH, and fondaparinux (Arixtra) for the initial treatment of VTE in cancer patients.¹²² A meta-analysis of 11 studies showed a statistically significant mortality reduction in patients treated with LMWH compared with those treated with UFH [relative risk (RR)=0.71, 95% CI, 0.52 to 0.98]. A meta-analysis of three studies comparing LMWH with UFH in reducing recurrent VTE was inconclusive (RR=0.78, 95% CI, 0.29 to 2.08). No data were available for bleeding outcomes, thrombocytopenia or postphlebotic syndrome. Fondaparinux showed a non-statistically significant benefit compared to UFH for death (RR = 0.52, 95% CI, 0.26 to 1.05). One study compared dalteparin to tinzaparin and showed a non-statistically significant mortality reduction with dalteparin (RR=0.86, 95% CI, 0.43 to 1.73). The study results support LMWH over UFH in the initial treatment of VTE cancer patients.

A meta-analysis of four randomized, double-blind, multicenter trials for prevention of VTE in 7,344 patients undergoing elective hip replacement, elective major knee surgery, and surgery for hip fracture compared SC fondaparinux 2.5 mg daily starting six hours after surgery to SC enoxaparin regimens.¹²³ Fondaparinux significantly reduced the primary efficacy outcome of VTE by day 11 compared with enoxaparin, 6.8 versus 13.7 percent, respectively (common odds reduction of 55.2 percent (95% CI, 45.8 to 63.1 percent; p<0.001). Fondaparinux as compared to enoxaparin resulted in increased risk of major bleeding, 2.7 versus 1.7 percent, respectively (p=0.008). However, the incidence of clinically relevant bleeding (leading to death or re-operation or occurring in a critical organ) did not differ between groups. In a post-hoc efficacy and safety analysis, the incidence of major bleeding was significantly less in patients receiving fondaparinux ≥ six hours versus < six hours following surgery (e.g. skin closure), 2.1 versus 3.2 percent, respectively.¹²⁴ There was no significant difference in the incidence of VTE at these different time points.

Efficacy of Injectable

Anticoagulants^{125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158}

Drug	Prophylaxis: Development of post-operative DVT (%)				Treatment: Recurrent VTE (%)
	Hip replacement	Knee replacement	Hip fracture surgery	Abdominal surgery	
dalteparin (Fragmin)	4-30	--	*30	3.9-4.4	*0-9
enoxaparin (Lovenox)	6-38	19-37	*19.1	9.7	3.3-4.1
fondaparinux (Arixtra)	1.7-5.6	12.5	8.3	4.2	3.9
tinzaparin (Innohep)	*21-31	*45	--	--	0-4.2

*off-label

Review of overall occurrence of DVT in patients undergoing orthopedic surgery does not reveal any significant advantage of one LMWH over another for prophylaxis. While fondaparinux (Arixtra) has been shown to reduce the development of post-operative DVT to a greater extent than enoxaparin, this risk reduction can be accompanied by an increase in risk of bleeding. Administration of fondaparinux before six hours after surgery has been associated with an increased risk of major bleeding.¹⁵⁹ After hemostasis has been established, the recommended timing of the first fondaparinux injection is six to eight hours after surgery.¹⁶⁰

Examination of data from VTE treatment trials reveals similar overlap in frequency of events as well as between-study variability.

Summary

The injectable anticoagulants, LMWHs and fondaparinux (Arixtra), are important treatment options in DVT and PE management. They offer advantages over UFH including lack of need for laboratory coagulation monitoring, ease of dosing, and reduced risk of heparin-induced thrombocytopenia (HIT). LMWHs have been shown to reduce mortality rates after acute DVT and provide similar efficacy. Initial therapy of PE with LMWH also appears as effective as UFH. When used in equipotent dosages, all of the LMWHs will provide a therapeutic anticoagulant effect.

Fondaparinux (Arixtra) has shown a reduction in preventing post-operative VTE compared to enoxaparin (Lovenox) following major orthopedic surgery (total hip replacement, total knee replacement, and hip fracture surgery). Fondaparinux (Arixtra) has been associated with an increased risk of bleeding; however, the timing of administration can affect the risk of bleeding. Fondaparinux (Arixtra) has been shown to be non-inferior to dalteparin (Fragmin) in preventing post-operative VTE in patients undergoing major abdominal surgery.

The Eighth American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines recommend extended-duration LMWH, fondaparinux (Arixtra), or warfarin for DVT prophylaxis in patients undergoing total hip replacement, knee replacement, or hip fracture surgery. For treatment of DVT or PE, the ACCP guidelines recommend anticoagulation with LMWH, fondaparinux (Arixtra), or warfarin for a minimum of three months.

Although each product has different FDA-approved indications, the ACCP makes no distinction among the agents for orthopedic surgery prophylaxis or treatment of VTE. While SC anticoagulants have subtle differences in methods of preparation, pharmacokinetic parameters, and anti-Xa activity, the clinical characteristics are similar.

The 2008 ACCP guidelines recommend long-term anticoagulation with warfarin in atrial fibrillation patients. The 2011 American Heart Association/American Stroke Association (AHA/ASA) stroke primary prevention guidelines recommend warfarin for all patients with nonvalvular atrial fibrillation, particularly those at high risk for stroke. Warfarin has been established for prevention of stroke in atrial fibrillation; however, it is associated with significant adverse events, genetic polymorphism, drug-drug and drug-food interactions, as well as laboratory monitoring.

Dabigatran is the first oral agent to show comparable efficacy and superiority over warfarin for stroke prevention in atrial fibrillation with similar to lower overall rates of major bleeding; however, long-term safety data are currently lacking. It offers a treatment alternative to adjusted-

dose warfarin in patients with nonvalvular atrial fibrillation. The 2011 American College of Cardiology, American Heart Association, and the Heart Rhythm Society (ACCF/AHA/HRS) focused update recommend dabigatran as an alternative to warfarin in AF and risk factors for stroke or systemic embolism without a prosthetic heart valve or hemodynamically significant valve disease, severe renal failure, or advanced liver disease. These guidelines do not recommend routinely switching patients to dabigatran who are already well maintained on warfarin. Dabigatran does not require laboratory monitoring or dose adjustments required with warfarin therapy. Ongoing trials are evaluating emerging oral therapies with comparable to better efficacy and improved safety, interactions, genetics, and therapeutic monitoring profiles.

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