



# Anticoagulants

## Therapeutic Class Review (TCR)

March 5, 2013

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## FDA-APPROVED INDICATIONS

Drug	Manufacturer	DVT prophylaxis				DVT Treatment*
		Hip replacement	Knee replacement	Hip fracture surgery	Abdominal surgery	
<b>Injectable</b>						
dalteparin (Fragmin®) <sup>1</sup>	Eisai	X	-	-	X	-
enoxaparin (Lovenox®) <sup>2</sup>	generic, Sanofi-Aventis	X	X	-	X	X (without PE in outpatient setting, with or without PE in inpatient setting)
fondaparinux (Arixtra™) <sup>3</sup>	GlaxoSmithKline	X	X	X	X	X
tinzaparin (Innohep®) <sup>4</sup>	Leo	-	-	-	-	X (inpatient setting only; with or without PE)
<b>Oral</b>						
apixaban (Eliquis®) <sup>5</sup>	Bristol-Myers Squibb	†	†	†	†	†
dabigatran (Pradaxa®) <sup>6</sup>	Boehringer Ingelheim	-	-	-	-	-
rivaroxaban (Xarelto®) <sup>7</sup>	Janssen	X	X	-	-	-
warfarin (Coumadin®) <sup>8</sup>	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

### ***apixaban (Eliquis)***

- to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF)

### ***dabigatran (Pradaxa)***

- to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF)

### ***rivaroxaban (Xarelto)***

- to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF). There are limited data on the relative effectiveness of rivaroxaban and warfarin in reducing the risk of stroke and systemic embolism when warfarin therapy is well-controlled
- for the treatment of deep vein thrombosis (DVT), pulmonary embolism (PE), and for the reduction in the risk of recurrence of DVT and of PE

### ***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 **apixaban**, dabigatran, rivaroxaban, and warfarin.

## **OVERVIEW**

Venous thromboembolism (VTE) is a significant public health problem in the United States. 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.<sup>9, 10</sup>

There are over 100,000 cases of PE diagnosed annually in the US. 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.<sup>11</sup>

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.<sup>12, 13</sup>

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 9<sup>th</sup> American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines published in February 2012, 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.<sup>14</sup> In patients undergoing orthopedic surgery (total hip replacement or knee replacement), DVT prophylaxis with LMWH, UFH, fondaparinux, vitamin K antagonist [(VKA) e.g., warfarin], or aspirin, and also the newer agents apixaban, dabigatran, and rivaroxaban (all Grade 1B) or an intermittent pneumatic compression device (IPCD) (Grade 1C) is recommended postoperatively for at least ten to fourteen days. LMWH is recommended over the other alternative agents (Grade 2B-2C). Limitations of alternative agents include the possibility of increased bleeding (which may occur with fondaparinux, rivaroxaban, and VKA), possible decreased efficacy (UFH, VKA, aspirin, and IPCD alone), and lack of long-term safety data (apixaban, dabigatran, and rivaroxaban). In patients undergoing hip fracture surgery, ACCP recommends use of one of the following for antithrombotic prophylaxis for a minimum of ten to 14 days: LMWH, fondaparinux, low-dose UFH, adjusted-dose VKA, aspirin (all Grade 1B), or an IPCD (Grade 1C). Apixaban (Eliquis) and dabigatran (Pradaxa) are not FDA approved for prophylaxis or treatment of venous thrombosis associated with orthopedic surgery.

Initial treatment options for VTE consist of either intravenous (IV) or subcutaneous (SC) UFH, SC LMWH or, fondaparinux for at least five days and until the international normalized ratio (INR) is in therapeutic range for at least 24 hours.<sup>15</sup> VKA therapy should overlap parenteral anticoagulant therapy, and should be initiated on the first treatment day. Rivaroxaban (Xarelto) also recently gained approval to treat DVT and PE; recommended duration of therapy is 21 days. LMWH or fondaparinux is suggested over UFH for the treatment of acute DVT of the leg, acute PE, or acute upper extremity DVT (UEDVT) of the axillary or more proximal veins (Grades 2B & 2C). In patients with DVT of the leg, or PE and no cancer, ACCP suggests VKA over LMWH for long-term therapy (Grade 2C); for patients with cancer, ACCP suggests LMWH over VKA (Grade 2B). Both VKA and LMWH are preferred over dabigatran or rivaroxaban for long-term therapy (Grade 2C). Apixaban (Eliquis) and dabigatran (Pradaxa) are not FDA approved for prophylaxis of venous thrombosis in patients without nonvalvular atrial fibrillation.

For patients with VTE secondary to a nonsurgical transient (reversible) risk factor, ACCP recommends anticoagulation therapy for three months.<sup>16</sup> For patients with first episode of unprovoked DVT or PE, anticoagulation is recommended for at least three months if there is a high bleeding risk (Grade 1B) and extended anticoagulation if low-moderate bleeding risk exists (Grade 2B). In patients with DVT of the leg who receive extended therapy, the guidelines suggest treatment with the same anticoagulant chosen for the first three months (Grade 2C). In patients with DVT of the leg who are treated with VKA, a therapeutic INR range of 2.0 to 3.0 (target INR of 2.5) for all treatment durations (Grade 1B) is

recommended. 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 twelve 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.<sup>17</sup> For long-term treatment, SC anticoagulants are an alternative therapy for patients in whom oral anticoagulants cannot be used.<sup>18</sup>

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 dosages.<sup>19</sup>

Atrial fibrillation (AF) is a common arrhythmia in clinical practice with an estimated prevalence of 0.4 percent to one percent.<sup>20</sup> The prevalence is higher in men than in women and with increasing age.<sup>21</sup> 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.<sup>22</sup> Ischemic stroke is the most frequent clinical manifestation of AF associated embolization and averages five percent annually in patients with nonvalvular AF.<sup>23</sup> In high-risk patients with AF, the annual stroke risk is six percent or greater, and patients strongly benefit from anticoagulation.<sup>24</sup> Due to the high risk of future ischemic stroke, the 2012 ACCP guidelines recommend long-term anticoagulation in patients with AF, including those with paroxysmal (intermittent) AF who have had a prior ischemic stroke, transient ischemic attack (TIA), or systemic embolism (Grade 1A).<sup>25</sup> For AF patients, including those with paroxysmal AF, with low risk of stroke, ACCP suggests no therapy (Grade 2B). For patients who do choose antithrombotic therapy, ACCP suggests aspirin (75 mg to 325 mg once daily) rather than oral anticoagulation (Grade 2B) or combination therapy with aspirin and clopidogrel (Grade 2B). In patients with intermediate or high risk of stroke, ACCP suggests dabigatran 150 mg twice daily over VKA (target INR range 2.0-3.0) (Grade 2B); oral anticoagulation over aspirin (75-325 mg once daily) or aspirin/clopidogrel (Grade 2B, 1B).

To prevent a secondary cardioembolic stroke in patients with a history of ischemic stroke or TIA and AF, ACCP suggests oral anticoagulation with dabigatran over VKA therapy (Grade 2B); for patients who are unsuitable for or choose not to take an oral anticoagulant, ACCP recommends combination therapy with ASA and clopidogrel (Grade 1B).

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.<sup>26</sup> It advises that 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 valvular disease, severe renal failure (creatinine clearance <15 mL/min), or advanced liver disease (impaired baseline clotting function) (Class I; Level of Evidence B).<sup>27</sup>

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. Apixaban (Eliquis) and rivaroxaban (Xarelto) were approved after these guidelines were released.

In patients with mechanical heart valves, warfarin therapy is recommended for long-term management (Grade 1A). The target INR and range vary based on the type of replacement heart valve present.<sup>28</sup>

According to the Center for Disease Control (CDC), stroke is the fourth leading cause of death behind heart disease, cancer, and chronic lower respiratory diseases.<sup>29</sup> There is consensus in the guidelines that warfarin should be given to high-risk patients with AF and aspirin should be given to patients deemed to be at low risk. According to the 2012 American Heart Association/American Stroke Association (AHA/ASA) warfarin (INR 2.0-3.0), dabigatran, rivaroxaban and apixaban are all indicated for the prevention of first and recurrent stroke in patients with nonvalvular AF and that the selection of these drugs should be individualized on the basis of risk factors, cost, tolerability, patient preference, potential for drug interactions and other clinical characteristics including time in the target INR range for those patients who have been taking warfarin.<sup>30</sup> They conclude that for patients with nonvalvular AF and at least one additional risk factor who have a creatinine clearance (CrCl) > 30 mL/min, dabigatran 150 mg twice daily is an efficacious alternative to warfarin (Class I; Level of Evidence B). The use of dabigatran 75 mg twice daily in these patients who have a CrCl 15 to 30 mL/min may be considered, but its safety and efficacy have not been established. There are no data to support the use of dabigatran in those with a CrCl < 15 mL/min. Rivaroxaban 20 mg daily is a reasonable alternative to warfarin in patients at moderate to high risk of stroke (prior TIA, stroke or systemic embolization or ≥2 additional risk factors), (Class IIa; Level of Evidence B). In those meeting these criteria but with a CrCl of 15 to 50 mL/min, rivaroxaban 15 mg daily may be considered, although its safety and efficacy have not been established. Rivaroxaban should not be used if the CrCl is < 15 mL/min. Apixaban is an efficacious alternative to aspirin in patients with nonvalvular AF deemed who are unsuitable for VKA (warfarin) therapy who have at least one additional risk factor (Class I; Level of Evidence B). Unresolved issues surrounding the use of the new anticoagulants include the lack of data comparing these drugs to one another (all were compared only to warfarin), the short duration of follow-up given the very long-term real-world indication, drug activity cannot be assessed in routine clinical practice which may lead to under- or over-treatment of patients, questionable safety of treatment for an acute ischemic stroke with a thrombolytic agent in patients receiving apixaban, dabigatran, or rivaroxaban, and the lack of an antidote in the setting of acute hemorrhage. Antiplatelet therapy with aspirin is recommended for low-risk and some moderate-risk patients with AF on the basis of patient preference, estimated bleeding risk if anticoagulated, and access to high-quality anticoagulation monitoring (Class I; Level of Evidence A). For patients with ischemic stroke or TIA with paroxysmal or permanent AF, anticoagulation with a VKA (INR 2–3) is recommended (Class I; Level of Evidence A). Aspirin monotherapy is recommended for patients unable to take oral anticoagulants (Class I; Level of Evidence A).

## 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 ease of SC route of administration. In addition, the incidence of thrombocytopenia appears to be lower with LMWH than with UFH.<sup>31</sup>

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).<sup>32</sup>

Dabigatran etexilate (Pradaxa) is an oral prodrug of dabigatran. Dabigatran and its active metabolites (acyl glucuronides) are competitive, direct thrombin inhibitors of both free and clot-bound thrombin. Dabigatran reversibly inhibits the active site of thrombin and 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.<sup>33, 34</sup> INR is relatively insensitive to the exposure to dabigatran and cannot be interpreted the same way as used for warfarin monitoring. The aPTT test provides an approximation of dabigatran's anticoagulant effect.

Apixaban (Eliquis) and rivaroxaban (Xarelto) are oral direct factor Xa inhibitors. These agents reversibly block the active site of factor Xa in a selective manner and do not require a cofactor (such as Anti-thrombin III) for activity.<sup>35,36,37</sup> Anticoagulant effect of apixaban and rivaroxaban cannot be monitored with standard laboratory testing (e.g. INR, aPPT).

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.<sup>38</sup>

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.<sup>39</sup>

## PHARMACOKINETICS<sup>40, 41, 42, 43, 44, 45, 46, 47</sup>

Drug	Bioavailability (%)	Half-life* (hrs)	Average molecular weight (daltons)	Anti-Xa : Anti-IIa activity	Peak Anti-Xa activity (hrs)
<b>Injectable</b>					
dalteparin (Fragmin) <sup>48</sup>	87	2-5	5,000	2-4 : 1	4
enoxaparin (Lovenox) <sup>49</sup>	~ 100	4.5-7	4,500	2.7-3.7 : 1	3-5
fondaparinux (Arixtra) <sup>50</sup>	~ 100	17-21	1,728	Anti-Xa only	3
tinzaparin (Innohep) <sup>51</sup>	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 (%)
<b>Oral</b>				
apixaban (Eliquis) <sup>52,53</sup>	50	12	O-demethylation and hydroxylation	Urine-27 Feces-50
dabigatran (Pradaxa) <sup>54</sup>	3-7	12-17	Esterase-catalyzed hydrolysis	Urine
rivaroxaban (Xarelto) <sup>55</sup>	80-100 (10 mg) 66 (20 mg)*	5-13	Oxidative degeneration	Urine-66 Feces-28
warfarin (Coumadin) <sup>56</sup>	100; with peak concentration generally reached within first 4 hours.	20-60 (mean 40)	Hepatic-primarily via CYP2C9	Urine-92 primarily as metabolites

\* The absolute bioavailability of rivaroxaban is dose-dependent. The estimated bioavailability for 10 mg dose is 80 to 100 percent and it is not affected by food. The absolute bioavailability for the 20 mg dose is approximately 66 percent in a fasted state and increases when administered with food. Both the 15 mg and 20 mg doses should be administered with food.

**CONTRAINDICATIONS/WARNINGS**<sup>57, 58, 59, 60, 61, 62, 63,64</sup>**Parenteral**

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 of LMWH or fondaparinux therapy should be considered before neuraxial intervention. Fondaparinux and LMWH are contraindicated in patients with active major bleeding as well as in patients with anti-platelet antibody associated thrombocytopenia. Thrombocytopenia of any degree should be monitored closely. If the platelet count falls below 100,000/mm<sup>3</sup> discontinuation of therapy should be considered. LMWH should be used with extreme caution in patients with heparin-induced thrombocytopenia (HIT); this is considered a contraindication for tinzaparin.

LMWHs are contraindicated in patients with hypersensitivity to any LMWH, UFH, or pork products. In addition, 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.

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

While tinzaparin (Innohep) should also not be given intravenously, none of the parenteral agents are intended for intramuscular administration.

These agents are primarily eliminated by the kidneys and should be used with caution in patients with renal insufficiency due to increased risk of major bleeding.

In patients with body weight less than 50 kg, fondaparinux is contraindicated when used for prophylaxis therapy with abdominal surgery, hip fracture surgery, or hip or knee replacement surgery and should be used with caution for treatment of PE and DVT due to increased risk of bleeding. Fondaparinux is also contraindicated in patients with bacterial endocarditis due to increased risk of bleeding. 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 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.

## Oral

**Apixaban (Eliquis)**, dabigatran (Pradaxa), rivaroxaban (Xarelto), and **warfarin** are contraindicated in patients with hypersensitivity to the product.

**Apixaban**, dabigatran, rivaroxaban, and warfarin increase the risk of bleeding and can cause serious and sometimes, fatal bleeding. Warfarin is contraindicated in patients with bleeding/hemorrhagic tendencies or blood dyscrasias. **Apixaban**, dabigatran, and rivaroxaban are contraindicated with active major or pathological bleeding. Concurrent use of the oral agents with drugs that increase the risk of bleeding (e.g., anti-platelet agents, heparin, fibrinolytic therapy, and chronic use of non-steroidal anti-inflammatory drugs [NSAIDs]) and labor and delivery can increase bleeding risk. Promptly evaluate any signs or symptoms of blood loss (e.g., a drop in hemoglobin and/or hematocrit or hypotension).

Bleeding is more likely to occur during drug warfarin initiation and dose escalation (resulting in a higher INR). Risk factors for bleeding include high intensity anticoagulation (INR >4), age ≥65 years, highly variable INRs, history of gastrointestinal (GI) bleeding, hypertension, cerebrovascular disease, serious heart disease, anemia, malignancy, trauma, renal insufficiency, and long duration of warfarin therapy.

Warfarin is contraindicated in pregnancy, except in women with mechanical heart valves, as it can cause congenital malformations, fetal hemorrhage, and spontaneous abortion. It is also contraindicated in situations of threatened abortion, eclampsia, and preeclampsia.

The manufacturers of **apixaban, dabigatran**, and rivaroxaban caution their use in pregnancy due to potential obstetric hemorrhage and/or emergent delivery.

Other warfarin contraindications include: recent or contemplated surgery of the central nervous system (CNS) or eye, or traumatic surgery resulting in large open surfaces, unsupervised patients with potential high levels of non-compliance, spinal puncture and other diagnostic or therapeutic procedures with potential for uncontrollable bleeding, major regional or lumbar block anesthesia, and malignant hypertension.

**Apixaban** and rivaroxaban carry boxed warnings that state that discontinuation of either agent in patients with nonvalvular AF places these patients at an increased risk of thrombotic events. If therapy

with apixaban or rivaroxaban must be discontinued for a reason other than pathological bleeding, consider administering another anticoagulant.

Although lapses in therapy should be minimized, dabigatran should be stopped one to two days before elective surgery in patients with CrCl  $\geq 50$  mL/min or three to five days prior in patients with CrCl  $< 50$  mL/min, to lessen bleeding risk. Longer lapses of dabigatran therapy may be necessary for patients undergoing major surgery, spinal puncture, or placement of a spinal or epidural catheter or port.

Dabigatran should not be used to prevent major thromboembolic events in patients with mechanical heart valves.<sup>65</sup> The European RE-ALIGN study was recently stopped because patients on dabigatran were more likely to experience strokes, myocardial infarction, and thromboembolism forming on the mechanical heart valves than those on warfarin. There was also more bleeding after valve surgery in the dabigatran users than in patients on warfarin.

Use of apixaban is not recommended in patients with prosthetic heart valves since safety and efficacy has not been studied in this population.

With regard to warfarin therapy in patients with prosthetic heart valves, INR target is dependent on the type and positioning of the specific valve.

Rivaroxaban carries a second boxed warning regarding the increased risk of spinal/epidural hematomas when neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is performed. 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 analgesics and patients concurrently on NSAIDs, platelet inhibitors, and other anticoagulants. Increased risk is also seen in those with a history of traumatic or repeated epidural or spinal puncture, spinal deformity, or spinal surgery. Frequent monitoring for signs and symptoms of neurologic impairment should be performed. The benefit and risk should be considered before neuraxial intervention in anticoagulated patients or patients to be anticoagulated for thromboprophylaxis. Epidural catheters should not be withdrawn earlier than 18 hours after the last rivaroxaban dose and the next dose should be held for at least six hours post removal. Withhold rivaroxaban for 24 hours following traumatic epidural or spinal puncture.

P-glycoprotein (P-gp) inhibition and renal insufficiency are major independent factors resulting in increased exposure to dabigatran and risk of bleeding. Renal function should be evaluated before initiating dabigatran and periodically throughout therapy. Discontinue dabigatran in patients who develop acute renal failure and consider alternate anticoagulation. Concomitant use of P-gp inhibitors in patients with renal impairment is expected to increase exposure to dabigatran above that observed with either factor alone. Dosage adjustments should be considered.

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 VKORC1 enzymes (which recycles vitamin K and is required for gamma carboxylation of vitamin K-dependent coagulation factors) 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 (< 0.1 percent) 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.

Do not use warfarin as initial therapy in patients with heparin-induced thrombocytopenia (HIT) and with or without thrombosis syndrome. 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. Treatment with warfarin may be considered after the platelet count has normalized.

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

### **Risk Evaluation and Mitigation Strategy (REMS)<sup>66</sup>**

A Risk Evaluation and Mitigation Strategy (REMS) is required for apixaban (Eliquis) and rivaroxaban (Xarelto) which includes a communication plan to inform healthcare professionals when discontinuing apixaban or rivaroxaban, an adequate alternative anticoagulant is needed to prevent an increased risk of thrombotic events (e.g. stroke) in patients with nonvalvular atrial fibrillation. Guidance on how to convert these patients from rivaroxaban to another anticoagulant is provided in the product label. The communication plan for rivaroxaban also advises that the 15 mg and 20 mg dosages should be taken with the evening meal.

### **DRUG INTERACTIONS<sup>67, 68, 69, 70, 71, 72, 73, 74</sup>**

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<sup>®</sup>), 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 (verapamil, amiodarone, quinidine, and clarithromycin) do not require dose adjustments. These results should not be extrapolated to other P-gp inhibitors. Exposure to dabigatran is higher when it is administered with dronedarone (Multaq<sup>®</sup>) or systemic ketoconazole than when it is administered alone. Consider reducing the dose of dabigatran to 75 mg twice daily when dronedarone or systemic ketoconazole is coadministered with dabigatran in patients with moderate renal impairment (CrCl 30-50 mL/min). The concomitant use of dabigatran and P-gp inhibitors in patients with severe renal impairment (CrCl 15-30 mL/min) should be avoided.

Apixaban (Eliquis) is a substrate of both CYP3A4 and P-gp enzymes. Inhibitors of CYP3A4 and P-gp increase exposure to apixaban and increase the risk of bleeding. Inducers of CYP3A4 and P-gp decrease exposure to apixaban and increase the risk of stroke. A dosage decrease to 2.5 mg twice daily of apixaban is advised when it is coadministered with strong dual inhibitors of CPY3A4 and P-gp (e.g. ketoconazole, itraconazole, ritonavir, clarithromycin). If a patient is already taking a dose of 2.5 mg

daily, avoid concomitant use with strong dual CYP3A3/P-gp inhibitors. Concomitant use of apixaban with strong dual inducers of CYP3A4 and P-gp (e.g. rifampin, carbamazepine, phenytoin) can decrease the exposure of apixaban and should be avoided. Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding.

Rivaroxaban (Xarelto) is neither an inhibitor nor an inducer of CYP450 enzymes. It is a substrate of both CYP3A4 and P-gp. Avoid concomitant use of rivaroxaban with combined P-gp and strong CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, ritonavir) as they increase rivaroxaban concentrations. In patients with renal impairment on concomitant combined P-gp and weak or moderate CYP3A4 inhibitors (e.g. amiodarone, diltiazem, dronedarone, felodipine, macrolides, quinidine, ranolazine, verapamil) avoid use unless the benefit outweighs the bleeding risk, since these patients may be at increased bleeding risk. Avoid concomitant use of rivaroxaban with combined P-gp and strong CYP3A4 inducers (e.g. carbamazepine, phenytoin, rifampin, St. John's wort) . Avoid use with other drugs that affect hemostasis such as anticoagulants, fibrinolytics, NSAIDs/aspirin, and antiplatelet drugs. Avoid concomitant use with clopidogrel unless the benefit outweighs the bleeding risk.

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.

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.

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. Inhibitors of CYP1A2, 2C9, and 3A4 may increase the exposure of warfarin, and hence increase its effect. Inducers of these enzymes may in turn decrease warfarin's effect.

CYP2C9 gene and VKORC1 gene variants generally explain the largest proportion of known variability in warfarin dose requirements. 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 more than one 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 eight to twenty percent, while the frequency of the CYP2C9\*3 variant is six to ten 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.

In addition, variants in the gene encoding vitamin K epoxide reductase complex 1 (VKORC1) may be responsible for approximately 25 to 30 percent of warfarin dose variances.<sup>75,76</sup> There are two main VKORC1 haplotypes: low-dose haplotype group (A) and a high-dose haplotype group (B). African Americans can have a higher proportion of group B haplotypes, and are on average relatively resistant to warfarin; while Asian Americans may have a higher proportion of group A haplotypes and are generally more sensitive to warfarin.

Exogenous administration of vitamin K, such as enteral feedings, certain multivitamins, and many foods, can decrease or reverse the activity of warfarin.<sup>77</sup> 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, brussels sprouts, leafy greens, asparagus, avocado, broccoli, cabbage, cauliflower, liver, soy products, lentils, peas, and green scallions. 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. Some botanicals may have anticoagulant, antiplatelet, and/or fibrinolytic properties (e.g., garlic and ginkgo biloba). These effects may be additive to the anticoagulant effects of warfarin. Conversely, some botanicals may decrease the effects of warfarin (e.g., co-enzyme Q10, St. John's wort, ginseng). Some botanicals and foods can interact with warfarin through CYP450 interactions (e.g., echinacea, grapefruit juice, ginkgo, goldenseal, St. John's wort).

In patients treated with warfarin, additional PT/INR determinations are recommended whenever other medications, including botanicals, are initiated, discontinued or taken irregularly.

## ADVERSE EFFECTS

Drug	Major bleeding	Thrombocytopenia	Injection site reactions
<b>Injectable</b>			
dalteparin (Fragmin) <sup>78</sup>	0-4.6	<1	2-12
enoxaparin (Lovenox) <sup>79</sup>	< 1-4	0.1-1.3	Reported
fondaparinux (Arixtra) <sup>80</sup>	2.2-3.4	0.04-3	Reported
tinzaparin (Innohep) <sup>81</sup> Treatment	0.8	0.13-1	16

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts, are not comparative, or all inclusive. 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.<sup>82</sup> Gastrointestinal complaints leading to discontinuation 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). In 2012, after review of new information the FDA concluded that bleeding rates associated with new use of dabigatran do not appear to be higher than bleeding rates associated with new use of warfarin, which is consistent with observations from the RE-LY trial.<sup>83</sup> FDA is continuing to evaluate multiple sources of data in the ongoing safety review of this issue.

The most serious adverse events reported with apixaban (Eliquis) in clinical trials were bleeding related.<sup>84</sup> The safety of apixaban 5 mg (n=11,284) and 2.5 mg (n=602) twice daily was evaluated in the ARISTOTLE and AVERROES studies. Mean duration of apixaban was 89 weeks for the ARISTOTLE and 59 weeks for AVERROES. Major bleeding was reported in 2.1 percent of patients on apixaban and 3.1 percent on warfarin (Hazard Ratio [HR] 0.69, 95% CI 0.6 to 0.8) p<0.0001). Clinically relevant nonmajor bleeding occurred in 2.1 percent and three percent of patients on apixaban and warfarin (HR 0.7, 95% CI 0.6 to 0.8) p<0.0001). Discontinuation due to bleeding-related adverse reactions in ARISTOTLE occurred in 1.7 percent and 2.5 percent of patients treated with apixaban and warfarin, respectively, and in AVERROES, in 1.5 percent and 1.3 percent of patients on apixaban and aspirin, respectively. In the ARISTOTLE study major bleeding did not differ based on age and weight.

Other adverse events reported for apixaban were hypersensitivity reactions and syncope in less than one percent of patients.<sup>85</sup>

The most common adverse event with rivaroxaban (Xarelto) for both DVT prophylaxis and in nonvalvular AF is bleeding. In DVT prophylaxis clinical trials the risk of bleeding was similar to that of enoxaparin (Lovenox) 40 mg once daily.<sup>86</sup> Major bleeding was seen in less than one percent of patients (for both hip and knee replacement surgery). During rivaroxaban treatment, the majority of major bleeding complications (≥60 percent) occurred during the first week after surgery. Alanine aminotransferase (ALT) greater than three times the upper limit of normal (ULN) was seen in 2.6 percent versus 3.8 percent of patients on rivaroxaban versus enoxaparin in the RECORD 1-3 trial. In the nonvalvular AF setting major bleeding, bleeding into a critical organ (mostly intracranial), fatal bleeding, bleeds resulting in transfusions, and GI bleeding was seen in 5.6 versus 5.4 percent, 1.3 versus 1.9, 0.4 versus 0.8 percent, 2.6 versus 2.1 percent, and 3.1 versus two percent of rivaroxaban versus warfarin patients, respectively. The most frequent adverse reactions associated with permanent drug discontinuation were bleeding events: 4.3 percent for rivaroxaban and 3.1 percent for warfarin.

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 (<0.1 percent).

There are no specific reversal agents for apixaban, dabigatran, or rivaroxaban. Fresh frozen plasma and red blood cells can be used for management of bleeding. Activated prothrombin complex concentrates, recombinant Factor VIIa, or concentrates of coagulation factors II, IX or X may be considered. The use of these agents has not been studied in clinical trials. Activated charcoal to reduce

absorption in case of apixaban or rivaroxaban overdose may be considered. Apixaban and rivaroxaban is not expected to be dialyzable, due to high plasma protein binding. Phytonadione (Vitamin K1) is the antidote for warfarin. Protamine is used as an antidote for LMWH and UFH. Dabigatran can be dialyzed; however, data supporting this approach are limited.

## SPECIAL POPULATIONS<sup>87, 88, 89, 90, 91, 92, 93,94</sup>

### 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.

Despite their unproven efficacy, LMWHs have rapidly become the anticoagulant of choice in many pediatric patients, both for primary prophylaxis and treatment of thromboembolism.<sup>95</sup> 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 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.<sup>96</sup>

The 2012 ACCP guidelines recommend anticoagulant therapy with either UFH or LMWH in children with DVT (Grade 1B). Initial treatment with UFH or LMWH should be for at least five days (Grade 1B).<sup>97</sup> 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 (Grade 1B). For ongoing therapy, the guidelines recommend LMWH or UFH. 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 to 12 months and at least three months, respectively (Grade 2C). In children with recurrent idiopathic VTE, ACCP recommends indefinite treatment with VKA (Grade 1A).

A study with 27 children evaluated enoxaparin for the treatment of DVT.<sup>98</sup> 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.<sup>99</sup> 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 apixaban (Eliquis), dabigatran (Pradaxa), rivaroxaban (Xarelto), and warfarin (Coumadin) 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 and more frequent PT/INR monitoring is recommended due to potential varying warfarin requirements.<sup>100</sup>

## Pregnancy

All four injectable agents in this class are Pregnancy Category B. Apixaban is also Pregnancy Category B. Dabigatran and rivaroxaban are Pregnancy Category C. Warfarin is Pregnancy Category X.

Warfarin is contraindicated in pregnancy, except in women with mechanical heart valves.

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.<sup>101</sup>

For pregnant patients, the 2012 ACCP guidelines recommend LMWH for the prevention and treatment of VTE, instead of UFH (Grade 1B).<sup>102</sup> For women receiving anticoagulation for the treatment of VTE who become pregnant, ACCP recommends LMWH over VKA during the first trimester (Grade 1A), in the second and third trimesters (Grade 1B), and during late pregnancy when delivery is near (Grade 1A). For women requiring long-term VKA who are attempting pregnancy and are candidates for LMWH substitution, ACCP recommends performing frequent pregnancy tests and substituting LMWH for VKA once patient is pregnant, instead of switching to LMWH while attempting to become pregnant (Grade 2C). For pregnant women, these guidelines recommend against oral direct thrombin (e.g., dabigatran) and anti-Xa (e.g., apixaban and rivaroxaban) inhibitors (Grade 1C).

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.<sup>103, 104</sup> 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.<sup>105</sup> There are only limited data available regarding the safety of fondaparinux (Arixtra) during pregnancy, therefore the 2012 ACCP guidelines recommend against its general use in pregnancy.<sup>106</sup>

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.<sup>107</sup> Based on data from 62 patients, there was no difference in mean BMD between the patients receiving dalteparin or the control group.

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.<sup>108</sup> 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.<sup>109</sup> The dose and/or frequency of administration of enoxaparin (Lovenox) should be reduced to once 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).

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  $\geq$  70 years with estimated CrCl  $\leq$  30 mL/min or patients  $\geq$  75 years with estimated CrCl  $\leq$  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 ( $p=0.035$ ), respectively, as were rates of confirmed VTE (2.6 versus 1.1 percent,  $p=0.34$ ). 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.<sup>110, 111</sup>

The 2012 ACCP guidelines suggest a reduced dose when LMWHs are used in patients with severe renal insufficiency (Grade 2C).<sup>112</sup>

Dosage adjustments are recommended for apixaban (Eliquis) in patients with serum creatinine  $\geq$  1.5 mg/dL and if the patient is at least 80 years of age or weighs 60 kg or less.

No dose adjustment of dabigatran is recommended in patients with a creatinine clearance [CrCl] > 30 mL/min. Dabigatran dosage should be reduced in patients with CrCl 15-30 mL/min to 75 mg twice daily. No dosing recommendations are available per the product label for patients with CrCl <15 mL/min or on dialysis. Renal function should be evaluated prior to the start of therapy and should be re-assessed in clinical situations associated with declining function. If acute renal failure develops, discontinue dabigatran. P-gp inhibition and impaired renal function both result in increased exposure to dabigatran. In patients with a CrCl 30ml/min to 50 mL/min, co-administration P-gp inhibitors (dronedaron or ketoconazole) may increase exposure similar to that observed in patients with severe renal impairment; consider reducing the dabigatran dosage to 75 mg twice daily. Avoid dabigatran and P-gp inhibitors in patients with severe renal impairment (CrCL 15-30 mL/min).

For DVT prophylaxis, rivaroxaban is not recommended in patients with severe renal impairment (CrCl <30 mL/min). It should be used with caution in patients with moderate renal impairment (CrCL 30 mL/min to < 50 mL/min); signs and symptoms of blood loss should be promptly evaluated. Discontinue rivaroxaban if acute renal failure develops. In nonvalvular atrial fibrillation, rivaroxaban is dosed based on creatinine clearance. In such patients avoid if CrCl < 15 mL/min.

Patients with renal failure have an increased risk of bleeding complications, therefore patients with moderate renal insufficiency who are taking warfarin should be monitored 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.

**Use of apixaban is not recommended in patients with severe hepatic impairment.**

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.

Avoid rivaroxaban in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment or with any hepatic disease with coagulopathy.

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 or older. The risk of stroke and bleeding increases with age, but the risk-benefit profile is favorable in all age groups.

In rivaroxaban clinical trials, no overall differences in effectiveness or safety were reported between patients < 65 years and those > 65 years of age. However, the elderly subjects exhibited an increase in drug exposure that may be caused by age-related changes in renal function.

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. Healthy Japanese subjects were found to have 20 to 40 percent higher rivaroxaban exposures compared to other ethnicities including Chinese. **However, these differences in exposure are reduced when values are corrected for body weight.**

## 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. Please see Drug Interaction section for more information.

## DOSAGES

### Parenteral

Drug	DVT prophylaxis					DVT treatment (outpatient)* §
	Hip replacement**	Knee replacement**	Hip fracture surgery**	Abdominal surgery	Medical	
<b>Injectable</b>						
dalteparin (Fragmin) <sup>113</sup>	5,000 units once daily for 5 to 10 days (up to 14 days given in clinical trials)	--	--	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) <sup>114</sup>	30 mg every 12 hours OR 40 mg once daily for 7 to 10 days (up to 14 days given in clinical trials)	30 mg every 12 hours for 7 to 10 days (up to 14 days given in clinical trials)	--	40 mg once daily for 7 to 10 days (up to 12 days given in clinical trials)	40 mg once daily for 6 to 11 days (up to 14 days given in clinical trials)	1 mg/kg every 12 hours
fondaparinux (Arixtra) <sup>115</sup>	2.5 mg daily for 5 to 9 days (up to 11 days given in clinical trials)	2.5 mg daily for 5 to 9 days (up to 11 days given in clinical trials)	2.5 mg daily for 5 to 9 days and up to 24 days (a total of 32 days (peri-operative and extended prophylaxis) was administered in clinical trials)	2.5 mg daily for 5 to 9 days (up to 10 days given in clinical trials)	--	Based on patient's weight: <50 kg: 5 mg daily 50-100 kg: 7.5 mg daily >100 kg: 10 mg daily
tinzaparin (Innohep) <sup>116</sup>	--	--	--	--	--	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 to 14 days and an extended thromboprophylaxis of up to 35 days after major orthopedic surgery in patients undergoing total hip replacement, hip fracture, or knee replacement surgery (Grade 2B).<sup>117</sup>

### 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/mm<sup>3</sup>) until the platelet count exceeds 100,000/mm<sup>3</sup>. Patients with platelet counts less than 50,000/mm<sup>3</sup> should not receive dalteparin until platelet count exceeds 50,000/mm<sup>3</sup>. Dose reductions are also necessary for patients with impaired renal function.

## Oral

The recommended dose of apixaban (Eliquis) is 5 mg twice daily.<sup>118</sup> A reduced dose of 2.5 mg twice daily is recommended in patients with at least two of the following: serum creatinine  $\geq$  1.5 mg/dL, age  $\geq$  80 years, and weight  $\leq$  60 kg. In addition, dosage reductions are recommended for those also on strong dual CYP3A4 and P-gp inhibitors. If a scheduled dose of apixaban is missed, the dose should be taken as soon as possible on the same day and twice daily administration should be resumed. The dose should not be doubled to make up for a missed dose. Apixaban should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding. Discontinue apixaban at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be non-critical in location and easily controlled.

When switching from warfarin to apixaban, warfarin should be discontinued and apixaban started when the INR is below 2. Apixaban affects INR, therefore, when switching from apixaban to warfarin, INR measurements during coadministration may not be useful for determining the appropriate dose of warfarin; therefore if continuous anticoagulation is necessary, discontinue apixaban and begin both a parenteral anticoagulant and warfarin at the time the next dose of apixaban would have been taken, discontinuing the parenteral anticoagulant when INR reaches an acceptable range. When switching between apixaban and anticoagulants other than warfarin, discontinue one being taken and begin the other at the next scheduled dose.

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.<sup>119</sup> 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.

The recommended dosage of rivaroxaban for DVT prophylaxis is 10 mg orally once daily without regard to food, starting six to ten hours post-op, after hemostasis has been established.<sup>120</sup> The duration of treatment for hip and knee replacement is 35 days and 12 days, respectively. Missed doses should be taken as soon as possible, on the same day and continued on the following day, with the usual once daily administration.

The recommended dosage of rivaroxaban for treatment of DVT and/or PE is 15 mg twice daily with food, for 21 days, followed by 20 mg once daily with food, for the remaining treatment. For the reduction of recurrence of DVT and/or PE rivaroxaban dosage is 20 mg once daily with food. Please see Pharmacokinetics section regarding rivaroxaban bioavailability with and without concomitant food intake.

For nonvalvular AF for patients with CrCl > 50 mL/min administer rivaroxaban 20 mg once daily with the evening meal. For nonvalvular AF for patients with CrCl 15-50 mL/min the recommended rivaroxaban dosage is 15 mg once daily with the evening meal. Avoid use in patients with CrCl < 15 mL/min. When switching from warfarin to rivaroxaban, discontinue warfarin and start rivaroxaban as soon as the INR is below 3.0 to avoid periods of inadequate anticoagulation. There is not a guide for converting patients from rivaroxaban to warfarin. Rivaroxaban affects INR, so INR measurements made during concomitant warfarin therapy may not be useful for determining the appropriate dose of warfarin. One approach may be to discontinue rivaroxaban and begin both a parenteral anticoagulant and warfarin at the time the next dose of rivaroxaban would have been taken.

The absorption of rivaroxaban is dependent on the site of drug release in the gastrointestinal (GI) tract (gastric versus small intestine or colon). Absorption is decreased significantly if given using a feeding tube which deposits drug in the proximal small intestine or further down the GI track. If a feeding tube is used for administration, confirm gastric placement.

Specific antidotes for apixaban, dabigatran, and rivaroxaban are not currently available. Oral or parenteral vitamin K1 reverses the anticoagulant effects of warfarin.

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 until 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.<sup>121</sup>

## Availability

Drug	Prefilled syringes	Vials
<b>Injectable</b>		
dalteparin (Fragmin) <sup>122</sup>	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) <sup>123</sup>	30, 40, 60, 80, 100, 120, 150 mg	100 mg/mL in 3 mL MDV (brand only)
fondaparinux (Arixtra) <sup>124</sup>	2.5, 5, 7.5, 10 mg	-
tinzaparin (Innohep) <sup>125</sup>	-	20,000 units/mL in 2 mL MDV

MDV = multiple-dose vial

Drug	Availability
<b>Oral</b>	
apixaban (Eliquis) <sup>126</sup>	2.5 mg, 5 mg tablets
dabigatran (Pradaxa) <sup>127</sup>	75 mg, 150 mg capsules
rivaroxaban (Xarelto) <sup>128</sup>	10, 15, 20 mg tablets
warfarin (Coumadin) <sup>129</sup>	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. Dabigatran must be kept in original bottles to protect from moisture. Open bottles of dabigatran have to be used within four months of being opened

Rivaroxaban 15 and 20 mg tablets can be crushed and mixed with apple sauce and immediately followed by food, for patients unable to swallow. Both strengths can also be crushed and administered via NG or gastric feeding tubes.

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 nonvalvular 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.<sup>130</sup> 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.<sup>131</sup> 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.<sup>132</sup> 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.<sup>133</sup> 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.<sup>134</sup> 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.<sup>135</sup> 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.<sup>136</sup> 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.<sup>137</sup> 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 ( $p=NS$ ). 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.<sup>138</sup> 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 ( $p=NS$ ). 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 ( $p=NS$ ). No major bleeding was observed.

### **dabigatran versus warfarin and placebo**

In two double-blind, randomized trials, dabigatran (150 mg twice daily) was compared with warfarin (active-control study) or with placebo (placebo-control study) in patients with VTE who had completed at least three initial months of therapy.<sup>139</sup> In the active-control study, recurrent VTE occurred in 26 of 1,430 patients in the dabigatran group (1.8 percent) and 18 of 1,426 patients in the warfarin group (1.3 percent) (HR dabigatran, 1.44; 95% CI, 0.78 to 2.64;  $p=0.01$  for noninferiority). Major bleeding occurred in 0.9 percent of patients in the dabigatran group and 1.8 percent of patients in the warfarin group (HR 0.52; 95% CI, 0.27 to 1.02). Major or clinically relevant bleeding occurred less frequently with dabigatran (HR, 0.54; 95% CI, 0.41 to 0.71). Acute coronary syndromes occurred in 0.9 percent of patients in the dabigatran group and 0.2 percent in the warfarin group ( $p=0.02$ ). In the placebo-control study, recurrent VTE occurred in 3 of 681 patients in the dabigatran group (0.4 percent) and 37 of 662 patients in the placebo group (5.6 percent) (HR, 0.08; 95% CI, 0.02 to 0.25;  $p<0.001$ ). Major bleeding occurred in 0.3 percent of patients in the dabigatran group and zero patients in the placebo group. Major or clinically relevant bleeding occurred in 5.3 percent of patients on dabigatran and 1.8 percent taking placebo (HR 2.92; 95% CI, 1.52 to 5.60). Acute coronary syndromes occurred in one patient each in the dabigatran and placebo groups. These studies were funded by the manufacturer of Pradaxa.

### **rivaroxaban (Xarelto) versus enoxaparin (Lovenox)**

Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism (RECORD) 1 and 2 for elective total hip replacement and RECORD 3 for elective total knee replacement were all randomized, double-blind, multinational trials that compared oral rivaroxaban 10 mg once daily started six to eight hours after wound closure to subcutaneous (SC) enoxaparin 40 mg once daily started 12 hours pre-op.<sup>140</sup> Enoxaparin 40 mg once daily is not the FDA-approved dose in knee replacement. In all these trials, rivaroxaban was superior in preventing total venous thromboembolism (VTE) (a composite endpoint of DVT, nonfatal PE, and death from any cause) and major VTE (a composite endpoint of proximal DVT, nonfatal PE, and venous thromboembolic death).

In RECORD 1 and 2, a total of 6,727 patients were randomized and 6,579 received study drug. In RECORD 1, the mean exposure duration ( $\pm$  SD) to rivaroxaban and enoxaparin was 33.3 + 7 and 33.6 + 8.3 days, respectively. In RECORD 2, the mean exposure duration to rivaroxaban and enoxaparin was 33.5 + 6.9 and 12.4 + 2.9 days, respectively. After day 13, oral placebo was continued in the enoxaparin group for the remainder of the double-blind study duration.

In RECORD 1, the occurrence of the primary efficacy outcome of total VTE at 36 days was 1.1 percent for rivaroxaban and 3.7 percent for enoxaparin ( $p<0.001$ ; absolute risk reduction 2.6 percent; 95% CI, 1.5 to 3.7, number needed to treat [NNT]=38).<sup>141</sup> The main secondary outcome of major VTE occurred in 0.2 percent of patients in the rivaroxaban group and in two percent of patients in the enoxaparin group ( $p<0.001$ , absolute risk reduction 1.7 percent, 95% CI, 1 to 2.5). The primary safety outcome of major bleeding occurred in 0.3 percent and 0.1 percent of patients in the rivaroxaban and enoxaparin groups respectively ( $p=0.18$ ).

In RECORD 2, the occurrence of the primary efficacy outcome of total VTE in the rivaroxaban versus enoxaparin groups was two percent versus 8.4 percent ( $p<0.001$ , absolute risk reduction 7.3 percent, 95% CI, 5.2 to 9.3, NNT=14).<sup>142</sup>

In RECORD 3 (n=2,531), the mean exposure duration ( $\pm$  SD) to rivaroxaban and enoxaparin was 11.9 + 2.3 and 12.5 + 3 days, respectively.<sup>143</sup> The primary outcome of total VTE 13 to 17 days after surgery occurred in 9.6 percent and 18.9 percent of patients treated with rivaroxaban and enoxaparin, respectively (p<0.001, absolute risk reduction 9.2 percent, 95% CI, 5.9-12.4, NNT=11). The secondary outcome of major VTE occurred in one percent of patients in the rivaroxaban group and 2.6 percent of patients in the enoxaparin group (p=0.01, absolute risk reduction 1.6 percent, 96% CI, 0.4-2.8). The primary safety outcome of major bleeding occurred in 0.6 percent and 0.5 percent of rivaroxaban- and enoxaparin-treated patients, respectively.

RECORD 4 (n=3,148) was a randomized, double-blind study comparing oral rivaroxaban 10 mg once daily to SC enoxaparin 30 mg every 12 hours (FDA-approved dose for knee replacement) in patients undergoing total knee replacement surgery.<sup>144</sup> The primary outcome (composite of DVT, PE, or death from any cause up to day 17 after surgery) occurred in 6.9 percent compared to 10.1 percent patients on rivaroxaban and enoxaparin, respectively (p=0.0118, absolute risk reduction 3.19 percent, 95% CI, 0.71-5.67, NNT=31). Major bleeding occurred in 0.7 percent of rivaroxaban patients compared with 0.3 percent of enoxaparin patients (p=0.1096).

## 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.<sup>145</sup> 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=NS). Major bleeding occurred in 1.2 percent of patients receiving enoxaparin and 1.1 percent of patients receiving fondaparinux (p=NS).

### *rivaroxaban (Xarelto) versus enoxaparin (Lovenox)*

Rivaroxaban therapy was compared to enoxaparin/VKA therapy for the treatment of DVT and/or PE and for the reduction in the risk of recurrence of DVT and/or PE in the EINSTEIN DVT (n=3,449) and EINSTEIN PE (n=4,832), open-label, non-inferiority studies.<sup>146,147,148</sup> Rivaroxaban was administered orally at an initial dose of 15 mg twice daily for three weeks, followed by 20 mg once daily; enoxaparin 1 mg/kg twice daily was administered subcutaneously for at least five days with VKA and VKA was continued once target INR (2.0-3.0) was achieved. Rivaroxaban was demonstrated to be non-inferior to enoxaparin/VKA for the primary composite endpoint of time to first occurrence of recurrent DVT or non-fatal or fatal PE [EINSTEIN DVT HR (95% CI): 0.68 (0.44, 1.04); EINSTEIN PE HR (95% CI): 1.12 (0.75, 1.68)]. Primary endpoint occurred in 2.1 percent of patients in the rivaroxaban groups for both EINSTEIN DVT and EINSTEIN PE, and occurred in 3.0 and 1.8 percent of patients in the rivaroxaban and enoxaparin/VKA groups, respectively. An extension study evaluated the risk of recurrence of DVT or PE in a double-blind fashion, comparing rivaroxaban (20mg daily) to placebo in patients (n=1,196) who had completed six to 14 months of treatment for DVT and/or PE. The primary composite endpoint of time to first occurrence of recurrent DVT or non-fatal or fatal PE was reported in 1.3 and 7.1 percent of patients on rivaroxaban and placebo, respectively (HR 0.18; 95% CI 0.09 to 0.39; p<0.0001).

### ***tinzaparin (Innohep) versus UFH***

A trial conducted by the American-Canadian Thrombosis Study Group compared tinzaparin with IV UFH for the treatment of PE.<sup>149</sup> 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.<sup>150</sup> It has established itself as a highly effective strategy for the treatment of VTE and is often used with UFH, LMWH, or fondaparinux.<sup>151</sup> Adjusted-dose warfarin has also demonstrated efficacy for the long-term prevention of VTE recurrence in most patients.<sup>152, 153</sup> Adjusted-dose warfarin has consistently established itself in randomized trials for prevention of stroke in younger (averaging about 70 years old) patients with nonvalvular atrial fibrillation.<sup>154, 155</sup> Adjusted-dose warfarin has shown superiority to aspirin by demonstrating 54 percent relative risk reduction of stroke in older nonvalvular atrial fibrillation patients ( $\geq 75$  years) with similar bleeding rates.<sup>156</sup> Dabigatran is the first oral anticoagulant to receive FDA-approval which, based on the RE-LY trial, has demonstrated similar to superior efficacy compared with warfarin for reduction of stroke and thromboembolism risk in patients with nonvalvular 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.<sup>157</sup> 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 adjusted-dose warfarin (INR target 2 to 3; unblinded). In the warfarin group, the mean percentage of the study period during which the INR was within the therapeutic range (INR 2 to 3) 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.<sup>158</sup> The rate of reporting clinical myocardial infarction was 0.7 per 100 patient-years for dabigatran versus 0.6 per 100 patient-years for warfarin. 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.<sup>159</sup> 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.<sup>160</sup> 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).<sup>161, 162</sup> In an analysis that compared bleeding risks in the RE-LY trial, at both doses dabigatran compared to warfarin had lower risks of intracranial and extracranial hemorrhage in patients less than 75 years old ( $p < 0.001$  for all).<sup>163</sup> In patients 75 years of age and older intracranial bleeding risk was lower for dabigatran versus warfarin but extracranial bleeding risk was similar or higher.

**Rivaroxaban Once-daily oral direct Factor Xa inhibition Compared with vitamin K antagonism for the prevention of stroke and Embolism Trial in Atrial Fibrillation (Rocket AF):**<sup>164</sup> This was a randomized, double-blind, multinational, Phase 3 trial in 14,264 patients with nonvalvular AF at increased risk for stroke. Patient risk factors included either two or more of the following: CHF, hypertension, age  $\geq 75$  years, diabetes; or a history of one of the following: stroke, TIA, or systemic embolus. The study compared once daily rivaroxaban to warfarin for the primary endpoint of non-inferiority for prevention of stroke and systemic embolism in nonvalvular AF. The median duration of the study was 590 days. Rivaroxaban was given at a dose of 20 mg once daily with the evening meal in patients with CrCl  $\geq 50$  mL/min and 15 mg once daily with the evening meal in patients with CrCl 30 to  $< 50$  mL/min. Warfarin was titrated to INR 2.0-3.0. Mean time in therapeutic range with warfarin was 55 percent.<sup>165</sup> Although in the as-treated safety population, the p value was significant ( $p < 0.02$ ) for rivaroxaban versus warfarin, in the intention-to-treat analysis, the composite primary endpoint was demonstrated for non-inferiority, but not for superiority to warfarin; composite primary endpoint of 3.8 percent compared to 4.3 percent for rivaroxaban compared to warfarin ( $p < 0.001$  for non-inferiority, HR 0.88, 95% CI 0.74-1.03;  $p = 0.12$  for superiority). Major and non-major bleeding was 14.9 percent/year versus 14.5 percent/year for rivaroxaban versus warfarin (HR 1.03, 95% CI 0.96-1.11;  $p = 0.44$ ). There was no difference in overall major and other clinically relevant bleeding between groups. Major bleeding, was seen in 5.6 versus 5.4 percent of rivaroxaban versus warfarin, respectively. More events were observed with transfusion hemorrhage (2.6 versus 2.1 percent,  $p < 0.045$ ) and GI bleed (3.1 versus two percent,  $p < 0.02$ ). Fewer events were observed with hemorrhage into a critical organ, mostly intracranial (1.3 versus 1.9 percent,  $p = 0.007$ ) and fatal bleeds (0.4 versus 0.8 percent,  $p = 0.003$ ), for rivaroxaban versus warfarin respectively. Intracranial bleeds alone were observed in 0.8 versus 1.2 percent of rivaroxaban and warfarin patients, respectively ( $p < 0.02$ ).

The ARISTOTLE trial was a randomized, double-blind study that compared apixaban 5 mg twice daily with dose-adjusted warfarin (target INR 2-3) in 18,201 patients with AF and at least one additional risk factor for stroke (age  $\geq 75$  years; previous stroke, TIA, or systemic embolism; symptomatic heart failure within the previous three months or LVEF  $\leq 40$  percent; diabetes mellitus; or hypertension requiring pharmacologic treatment).<sup>166,167</sup> The dose of apixaban was reduced (2.5 mg twice daily) in patients with at least two of the following characteristics: age  $\geq 80$  years, body weight  $\leq 60$  kg, or serum creatinine  $\geq 1.5$  mg/dL. The median duration of follow-up was 1.8 years. Mean age of was 69 years. The primary outcome of ischemic or hemorrhagic stroke or systemic embolism occurred in 1.27 percent per year in the apixaban group, and 1.6 percent per year in the warfarin group (HR for apixaban 0.79, 95% CI 0.66 to 0.95;  $p < 0.001$ ). The rate of hemorrhagic stroke was 0.24 percent per year

in the apixaban group, as compared with 0.47 percent per year in the warfarin group (HR 0.51; 95% CI, 0.35 to 0.75;  $p < 0.001$ ), and the rate of ischemic or uncertain type of stroke was 0.97 percent per year in the apixaban group and 1.05 percent per year in the warfarin group (HR 0.92; 95% CI, 0.74 to 1.13;  $p = 0.42$ ). Apixaban was found to be superior to warfarin in preventing stroke or systemic embolism, primarily attributable to a reduction in hemorrhagic stroke and ischemic strokes with hemorrhagic conversion compared to warfarin. Purely ischemic strokes occurred with similar rates on both drugs. The primary safety outcome of major bleeding occurred in 2.13 percent per year in the apixaban arm, and 3.09 percent per year in the warfarin arm. The ARISTOTLE trial was funded by the manufacturers of apixaban.

The AVERROES study randomized 5,599 patients with AF who were at increased risk for stroke and who were not candidates for warfarin therapy, to receive apixaban 5 mg twice daily (or 2.5 mg twice daily in selected patients) or aspirin 81 mg to 324 mg daily. Mean duration of follow-up was 1.1 years. The primary outcome was occurrence of stroke or systemic embolism.<sup>168,169</sup> Fifty-one primary outcome events (1.6 percent per year) occurred in the apixaban group and 113 events (3.7 percent per year) in the aspirin group. Forty-four cases (1.4 percent per year) of major bleeding were reported with apixaban use, and 39 (1.2 percent per year) with aspirin use; there were 11 cases of intracranial bleeding with apixaban and 13 with aspirin. AVERROES was stopped early based on a prespecified interim analysis that reported a significant reduction in stroke and systemic embolism for apixaban compared to aspirin that was associated with a modest increase in major bleeding. The AVERROES trial was funded by the manufacturers of apixaban.

## META-ANALYSIS

Two different meta-analyses evaluated the randomized, controlled trials of LMWH versus UFH in the treatment of acute DVT.<sup>170, 171</sup> 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.<sup>172</sup> A meta-analysis of 11 studies showed a statistically significant mortality reduction at three months of follow-up 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 showed no statistically significant reduction (RR=0.78, 95% CI, 0.29 to 2.08). The overall quality of evidence was low for LMWH compared to UFH due to imprecision and potential publication bias. There were no statistically significant differences between UFH and fondaparinux for death (RR 1.27; 95% CI 0.88 to 1.84), recurrent VTE (RR 0.95; 95% CI 0.57 to 1.60), major bleeding (RR 0.79; 95% CI 0.39 to 1.63) or minor bleeding (RR 1.50; 95% CI 0.87 to 2.59). 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.<sup>173</sup> 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  $\geq$  six hours versus  $<$  six hours following surgery (e.g. skin closure), 2.1 versus 3.2 percent, respectively.<sup>174</sup> There was no significant difference in the incidence of VTE at these different time points.

A systematic review evaluated randomized controlled trials of dabigatran (150 mg and 220 mg daily) and rivaroxaban (10 mg daily) compared with enoxaparin (40-60 mg daily) in elective orthopedic surgery.<sup>175</sup> Hemorrhagic events were defined as major and clinically relevant non-major bleeds. Rivaroxaban was superior to enoxaparin for the prevention of VTE (RR 0.56, 95% CI 0.43-0.73,  $p < 0.0001$ ), with a non-significant trend for increased hemorrhage (RR 1.26, 95% CI 0.94-1.69,  $p = 0.13$ ). Dabigatran was not superior to enoxaparin for prevention of VTE (RR 1.12, 95% 0.97-1.29,  $p = 0.12$ ). Dabigatran did not reduce hemorrhage risk (RR 1.10, 95% 0.90-1.35,  $p = 0.32$ ). Adjusted indirect comparison for the pooled relative risks showed that rivaroxaban was superior to dabigatran in preventing VTE, RR 0.5 (95% CI 0.37-0.68), but with a slight trend towards increased hemorrhage RR 1.14 (95% CI 0.80-1.64).

A meta-analysis evaluated seven trials ( $n = 30,514$ ) of dabigatran that reported on MI or ACS as secondary outcomes, including two stroke prophylaxis in atrial fibrillation studies, one in acute VTE, one in ACS, and three short-term prophylaxis of DVT.<sup>176</sup> In the studies dabigatran was compared to control arms (warfarin, enoxaparin, or placebo). Dabigatran was significantly associated with a higher risk of MI or ACS compared with the controls (dabigatran, 1.19 percent versus control, 0.79 percent; OR 1.33; 95% CI, 1.03-1.71;  $p = 0.03$ ). The risk of MI or ACS was similar when using revised RE-LY trial results (OR 1.27; 95% CI, 1-1.61;  $p = 0.05$ ) or after exclusion of short-term trials (OR 1.33; 95% CI, 1.03-1.72;  $p = 0.03$ ).

### Efficacy of Injectable Anticoagulants<sup>177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210</sup>

Drug	Prophylaxis: Development of post-operative DVT (%)				Treatment: Recurrent VTE (%)
	Hip replacement	Knee replacement	Hip fracture surgery	Abdominal surgery	
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.<sup>211</sup> After hemostasis has been established, the recommended timing of the first fondaparinux injection is six to eight hours after surgery.<sup>212</sup>

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 9<sup>th</sup> American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines recommend LMWH, fondaparinux (Arixtra), UFH, warfarin, aspirin, apixaban (Eliquis), dabigatran (Pradaxa), or rivaroxaban (Xarelto) for DVT prophylaxis in patients undergoing total hip or knee replacement surgery. LMWH is recommended over the other alternatives. For VTE prophylaxis in patients undergoing hip fracture surgery, ACCP recommends LMWH, fondaparinux, low dose unfractionated heparin, warfarin, aspirin or an intermittent pneumatic compression device. For treatment of DVT or PE, the ACCP guidelines recommend anticoagulation with IV unfractionated heparin, SC LMWH, or fondaparinux (Arixtra), or warfarin for a minimum of three months. While SC anticoagulants have subtle differences in methods of preparation, pharmacokinetic parameters, and anti-Xa activity, the clinical characteristics are similar. Rivaroxaban (Xarelto) recently gained approval to treat DVT and PE; recommended duration of therapy is 21 days.

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. The 2012 ACCP guidelines recommend long-term anticoagulation with dabigatran (Pradaxa) over warfarin in patients with intermediate or high risk of stroke, in atrial fibrillation patients. The 2012 AHA/ASA update added the newer anticoagulants apixaban, dabigatran and rivaroxaban, to previously recommended warfarin for prevention of first or recurrent stroke in patients with nonvalvular atrial fibrillation. Dabigatran and apixaban are appropriate alternatives in specific patients with at least one additional risk factor. Rivaroxaban is an appropriate alternative in those at moderate to high risk of stroke (e.g. history of TIA, stroke, or  $\geq$  two additional risk factors).

Twice-daily dabigatran (Pradaxa) is the first oral agent to show comparable efficacy and superiority over warfarin for stroke prevention in nonvalvular 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. Recommendations for apixaban (Eliquis) and rivaroxaban (Xarelto) were not available.

Rivaroxaban (Xarelto) has shown superiority to enoxaparin in prevention of DVT/PE in elective hip and knee replacement surgery, with a similar safety profile; however long-term safety data are currently lacking. It offers a once-daily oral option for VTE prophylaxis in this orthopedic population.

Rivaroxaban (Xarelto) has shown non-inferiority to warfarin for prevention of stroke and systemic embolism in nonvalvular atrial fibrillation. There were no significant differences in overall major and non-major clinically relevant bleeding, with significantly lower rates of intracranial hemorrhage and fatal bleeding and more events of gastrointestinal bleeding and transfusions hemorrhage. However long-term safety and efficacy data are currently lacking. It offers a once-daily treatment alternative to adjusted-dose warfarin in patients with nonvalvular atrial fibrillation.

Twice-daily apixaban was found to be superior to warfarin in preventing stroke or systemic embolism and was associated with less bleeding in the ARISTOTLE study, and was favored over aspirin therapy in reducing stroke or systemic embolism with a modest increase in major bleeding in the AVERROES study.

Apixaban, dabigatran and rivaroxaban do not require laboratory monitoring and associated dose adjustments required with warfarin therapy. None of these new anticoagulants have an antidote currently available.

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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