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# Anticoagulants and Applicable Disease States for Pharmacy Technicians

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## LEARNING OBJECTIVES

*Upon completion of this module, the subscriber will be able to:*

1. Describe the common signs and symptoms of stroke, deep vein thrombosis, and pulmonary embolism.
2. Recognize the importance of potential drug and dietary interactions with this class of medications.
3. Discuss the common adverse effects of anticoagulation agents.
4. List available dosage forms and appropriate storage and handling for anticoagulants.
5. Outline the goals of medication therapy (pharmacotherapy) in patients with diagnoses requiring anticoagulation therapy.



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# Anticoagulants and Applicable Disease States for Pharmacy Technicians

## INTRODUCTION

Anticoagulation therapy is used in the prevention and treatment of blood clots associated with many disease states, surgeries, and medical conditions. The ultimate goal of this class of medications is to prevent venous thromboembolism (VTE) events, or blood clots.

VTE events are common in the United States (U.S.); as many as 300,000 to 600,000 people each year are diagnosed with a deep vein thrombosis (DVT) or pulmonary embolism (PE).<sup>1</sup> Within that population, it is estimated up to 100,000 may die as a result.<sup>2</sup> Atrial fibrillation (AF) is the most common heart arrhythmia and has been identified as the largest independent risk factor for stroke.<sup>3</sup> Stroke, the leading cause of death in the U.S.,<sup>4</sup> costs an estimated 38.6 billion dollars per year in health care services, medications, and missed days from work.<sup>5</sup>

Whether the technician's practice site is in a hospital or retail setting, they are likely to be involved with a medication from this class on a daily basis, if not multiple times per day. Anticoagulants are frequently cited as the most common drugs to cause Adverse Drug Events (ADEs).<sup>6</sup> Many statistics describe the impact of this on patients; however, the most clinically significant figure is that about 70% of anticoagulant ADEs are potentially preventable.<sup>6</sup> This is where the pharmacy technician can have an impact. Due to the large number of anticoagulants available, and the likelihood for serious adverse effects, the technician can potentially assist in reducing life threatening errors by increasing their knowledge and familiarity with this class of drugs. Their attentiveness while working with these products will help ensure the best outcomes for the patient.

## DISEASE STATES

### Deep Vein Thrombosis/Pulmonary Embolism

Blood clots (referred to as deep vein thrombosis) can develop in the arms, or more commonly, in the veins of the legs. If the blood clot breaks off of the vein wall in the extremity, it can travel through the blood stream and become lodged in

a lung, resulting in a pulmonary embolism. The term VTE encompasses a diagnosis of DVT, PE, or both.<sup>7</sup>

Several risk factors have been identified for developing a DVT and/or a PE. Some risks are reversible (meaning patients can modify their risk by adjusting their activity and/or behaviors) while others are not, such as gender specific risks. All risk factors are listed in **Table 1**.<sup>7,8</sup>

Many patients with a DVT are often diagnosed after presenting to a doctor or hospital complaining of any of the following: extreme swelling in the affected arm or leg, persistent pain that worsens over days, or discoloration (redness) of the limb. One warning sign a patient may have a PE is extreme and unexplained shortness of breath. These patients may also report chest discomfort.<sup>7</sup> Possible ways to diagnosis a patient with a VTE event include blood tests, an ultrasound, and/or a computed tomography (CT) scan.

### Stroke/Transient Ischemic Attack

A stroke, or cerebrovascular accident (CVA), is a medical emergency defined as the rapid loss of brain function due to a loss in the blood supply to the brain.<sup>9</sup> Fewer Americans die now from stroke than they did even 15 years ago- possibly due to increased awareness and better control of certain risk factors.<sup>9</sup> Age is the single most important risk factor. For each successive 10 years after the age of 55, the stroke rate more than doubles for men

**Table 1. Risk Factors for Venous Thromboembolism (VTE)<sup>7,8</sup>**

Cancer
Inherited Thrombophilic Disorders
Obesity
Oral Contraceptive/Hormone Replacement Therapy Use
Pregnancy
Prolonged Immobilization
Surgery
Trauma

and women.<sup>10</sup> Stroke incidence rates are higher in men, but because women usually live longer, more females die of stroke each year.<sup>10</sup> For a complete list of risk factors for stroke, see **Table 2**.<sup>9,10</sup>

A transient ischemic attack (TIA) is also caused by a clot in the brain.<sup>11</sup> The only difference between a stroke and a TIA is that the blockage of blood flow to the affected part of the brain is temporary.<sup>11</sup> A TIA is commonly referred to as a mini-stroke because the symptoms are very similar to those of a stroke.<sup>11</sup> However, these TIA symptoms usually only last for an average of less than 5 minutes.<sup>11</sup> When the TIA symptoms have disappeared, there is not usually any lasting damage to the brain.<sup>11</sup> It is important to stress that although a TIA appears to be less dangerous than a stroke, it is still a medical emergency.<sup>11</sup>

If it is suspected someone is having a stroke or TIA, the American Heart Association advises calling 9-1-1 as the first response to possible stroke or TIA symptoms.<sup>12</sup> The acronym F.A.S.T. has been adapted to promote stroke detection and appropriate response. See **Table 3** for a more in depth explanation. Once the patient arrives at the hospital, they will likely undergo several tests (blood, CT scan, and/or magnetic resonance imaging [MRI]) to confirm a diagnosis of a stroke or TIA.<sup>10</sup>

### Atrial Fibrillation (AF)

Atrial fibrillation is a heart arrhythmia characterized by rapid, disorganized contraction of the heart's two upper chambers. These chambers are called the atria.<sup>13</sup> The term fibrillation means to contract very fast and irregularly. Normally, blood empties from the atria into the lower two chambers of the heart. However, in patients with AF, the arrhythmia causes the blood in the atria to pool, thereby increasing the chance a blood clot could form and result in a stroke.

Cigarette Smoking	Increasing Age
Diabetes	Obesity
Heart Disease	Obstructive Sleep Apnea
Heavy or Binge Drinking	Personal or Family History of Stroke
High Blood Pressure	Race (African Americans have the highest risk)
High Cholesterol	Use of Illicit Drugs (i.e. cocaine)

AF is caused by electrical issues in the heart. Damage to the electrical system can be the result of other conditions that affect the heart, such as high blood pressure and coronary heart disease.<sup>13</sup> Also, inflammation is thought to play a role in the destruction of the electrical system.<sup>14</sup> Some people who have AF are unaware, as they do not have any signs or symptoms of the arrhythmia. Others may present with one or more of the following complaints: palpitations (a sensation described as the heart skipping a beat, fluttering, and/or beating too hard/fast), shortness of breath, weakness or problems exercising, chest pain, dizziness or fainting, tiredness, or confusion.<sup>13</sup> As AF sometimes does not cause signs or symptoms, it may be found when testing for other conditions or during a physical exam. An electrocardiogram (EKG) or a Holter Monitor evaluation are considered the gold standard in diagnosing AF.<sup>15</sup>

### Heart Valve Replacements

The valves in your heart have two major functions. The first is to allow the blood to flow smoothly throughout the heart. The second, more important function, is to prevent the blood from flowing backwards in the circulatory system.<sup>16</sup> The risks, signs and symptoms, and diagnostic procedure for these patients requiring heart valve replacement surgery are beyond the scope of this module. However, it is important to note, following the replacement of the aortic or mitral valve, the risk for developing a blood clot is present.<sup>17</sup>

<b>F</b>	<b>Face Drooping</b> Does one side of the face droop or is it numb? Ask the person to smile. Is the person's smile uneven?
<b>A</b>	<b>Arm Weakness</b> Is one arm weak or numb? Ask the person to raise both arms. Does one arm drift downward?
<b>S</b>	<b>Speech Difficulty</b> Is speech slurred? Is the person unable to speak or hard to understand? Ask the person to repeat a simple sentence, like "The sky is blue." Is the sentence repeated correctly?
<b>T</b>	<b>Time to Call 9-1-1</b> If someone shows any of these symptoms, even if the symptoms go away, call 9-1-1 and get the person to the hospital immediately. Check the time so you'll know when the first symptoms appeared.

## Percutaneous Coronary Intervention

Currently, there are two main treatment choices for patients who suffer from chest pain (angina): medication and intervention. The first intervention type is usually an angioplasty, or percutaneous coronary intervention (PCI). During this procedure, performed at a hospital, a catheter is used to open narrowed heart arteries and a stent (tube) is usually placed in the artery to keep it open and restore blood flow to the heart.<sup>18</sup> During the PCI, there is an increased risk for a clot forming which may make it necessary to use an anticoagulant during the procedure.<sup>18</sup> Additional risk factors and treatment options exist, but are too in depth for this module.

### *Test Your Knowledge #1:*

List the risk factors for VTE.

1. \_\_\_\_\_
2. \_\_\_\_\_
3. \_\_\_\_\_
4. \_\_\_\_\_
5. \_\_\_\_\_
6. \_\_\_\_\_
7. \_\_\_\_\_
8. \_\_\_\_\_

*Answers on page 24.*

## TREATMENT

Due to the wide array of disease states and patients requiring VTE treatment or prevention, numerous medications have been studied and approved to meet the demand. Some medications are exclusively used for one indication, while other medications may be used to treat a number of conditions discussed above. The long term goal(s) of therapy for all patients can be summarized by the following: reducing the risk of a VTE event and/or lessening the risk of, or preventing a stroke.

### Non-Pharmacological

In addition to anticoagulants, non-pharmacological (non-medication) strategies can be used in certain situ-

ations to aid in the prevention of a VTE/stroke, or they can be employed in the treatment of different conditions. Many anticoagulants have contraindications associated with their use. If it is determined the patient does not meet criteria for a medication, the patient may then be required to utilize a non-pharmacologic treatment. The patient may also have input and may elect not to utilize medications and prefer an alternate management approach. Certain risk factors and surgeries may increase the risk for an event, but only slightly, and the recommended prevention approach may be a non-pharmacological intervention.

### *Inferior Vena Cava Filter*

Medical agents are usually preferred for the treatment of DVT. However, the placement of an inferior vena cava (IVC) filter can be considered for patients who cannot use conventional therapies due to active bleeding or drug interactions.<sup>19</sup> The goal of these filters is to prevent a PE by “catching” a clot that has broken off of a DVT in an arm or leg. These filters can be placed in the body using minimally invasive techniques. Although no procedure is without risk, this is a common treatment used in the U.S., as an estimated 49,000 filters are placed each year.<sup>20</sup> Some filters are inserted with the intention of removal in a short amount of time, while others can be left in for life. Robust evidence indicates the use of these filters effectively reduces the risk of a PE.<sup>21</sup>

### *Graduated Compression Stockings and Intermittent Pneumatic Compression Devices*

For patients admitted to a hospital, two mechanical methods are available to prevent the formation of a DVT in the legs. The graduated compression stocking (GCS) works by reducing the pooling of blood in the deep veins of the legs by applying greater pressure at the ankle rather than higher.<sup>22</sup> This sock-like device comes in two lengths, thigh-level or below-knee. Intermittent pneumatic compression (IPC) devices are placed on the legs to promote blood return from the leg to the heart by cyclical inflation and deflation of the apparatus.<sup>23</sup> These two devices are routinely used before, during, and after surgery, as well as for patients who are actively bleeding.<sup>22</sup> These devices can be used during a hospital stay in addition to medications to further lessen the risk of developing a VTE.

## Pharmacological

Many people refer to anticoagulants as “blood thinners.” However, these medications do not thin the blood; rather, they cause the blood to take longer to clot. Choosing the best anticoagulant may be tough for clinicians, as they have to analyze the risks and benefits for each medication available. The ideal anticoagulant prevents the VTE or stroke (meets its indication) and has the smallest risk of bleeding, or other undesirable effects. Not all anticoagulants have been studied in every disease state; therefore, many medications are marketed to niche indications. The best anticoagulant is usually selected by looking at patient-specific factors, as well as evaluating evidence in the medical literature.

The goals of medication therapy in patients with diagnoses requiring anticoagulation therapy include: selecting the best anticoagulant for each patient taking into account patient preferences and medical history; using the appropriate dose of each anticoagulant to ensure effectiveness; and minimize the potential risk(s) for adverse drug events and errors to protect the patient from a safety standpoint.

### *Test Your Knowledge #2:*

Name the non-pharmacological VTE prevention strategies.

1. \_\_\_\_\_
2. \_\_\_\_\_
3. \_\_\_\_\_

*Answers on page 24.*

## ADVERSE EVENTS AND SAFETY INFORMATION

The next section of the module will highlight key information about each anticoagulant. However, it is important to stress the most common and potentially most severe side effect with any anticoagulant is bleeding.<sup>24,25</sup> The reaction(s) can differ in terms of severity, from a bruise caused by bumping into an object or a life threatening bleed in a patient’s brain.<sup>25</sup> While each drug discussed below has other potential adverse events, to identify them all and report the incidence is beyond the scope of this

module. However, a few side effects are given for each medication for completeness. It is important to note, these medications do not cause spontaneous bleeding when used appropriately; however, if the patient is bleeding, the anticoagulant could make the situation worse.

Patients should be aware of, and seek medical attention if, they pass blood in the urine or stools. Urine with blood in it will appear to be orange or red in color. The patient may note bright red blood when having a bowel movement, or find dark, tarry stools.<sup>26,27</sup> Both are visual indicators of internal bleeding.

Patients could also have an increased number and frequency of bruises. Bruises that are severe, do not improve and/or get worse, or are unexplained are also worrisome and should be checked by a clinician.<sup>26,27</sup> Coughing up blood, blood in vomit, and prolonged nose bleeds (lasting longer than 10-15 minutes) also warrant a trip to a doctor or an emergency room.<sup>26,27</sup>

While these have all been bleeding events that are noticeable, there are some bleeding events which may not be seen. If a patient on an anticoagulant complains of severe or unusual headaches, this could be a sign of an intracranial hemorrhage (bleeding in the brain).<sup>26,27</sup> If a patient on any anticoagulant falls or sustains trauma to the head, it is encouraged the patient be evaluated as soon as possible to rule out an intracranial hemorrhage.<sup>26,27</sup>

For other general safety tips or recommendations for patients on anticoagulants, see **Table 4** (on page 7).<sup>26,27</sup> Certain independent risk factors have been identified which increase a patient’s risk for bleeding. Some of these risk factors are: advanced age; previous history of a bleed; certain concomitant medication use; and kidney and liver impairment.<sup>24</sup>

## Oral Medications

### *Vitamin K Antagonists*

Warfarin (Coumadin) is the most commonly prescribed outpatient anticoagulant.<sup>28</sup> For over 50 years, this agent was the only available oral anticoagulant on the market.<sup>29</sup> Warfarin works by limiting the body’s ability to form blood clots by inhibiting the production of vitamin K-dependent clotting factors. These clotting factors are some of the many substances used to form a clot.<sup>30</sup>

This medication requires rigorous monitoring and dose adjustments. Patients taking this medication will have

**Table 4. Safety Tips for Patients on Anticoagulants<sup>26,27</sup>**

- Take the medication at the same time each day.
- Never skip a dose and never take a double dose without checking with a clinician.
- Check with your doctor or pharmacist before starting any nonprescription or over-the-counter drugs (especially ones that contain aspirin or nonsteroidal anti-inflammatory drugs such as ibuprofen or naproxen).
- If indicated, be sure to get your blood tested as recommended by the clinician prescribing the anticoagulant.
- Before any surgery or test, discuss with the doctor performing the procedure if you need to stop your anticoagulant. Do NOT stop these medications without discussing with a clinician first.
- Be alert for any signs or symptoms of bleeding and call your primary care doctor or seek emergency treatment if noted.
- Wear a medical identification bracelet informing others you are taking an anticoagulant.

blood tests done frequently at an anticoagulation clinic, laboratory, or physician's office. The test measures how long it takes for the sample of blood to form a clot and is referred to as the protime (PT).<sup>30</sup> The protime is used in a calculation to determine the patient's international normalized ratio (INR).<sup>30</sup> Target ranges for patients with AF, DVT, and PE are INR of 2.0 – 3.0.<sup>31</sup> For patients with certain heart valve replacements, a higher range of 2.5 – 3.5 is targeted.<sup>31</sup> An INR below the target range indicates the patient needs more warfarin, and conversely, an INR above the range implies a lower dose is necessary. Since there is not a fixed dose of warfarin, the appropriate dose for each patient is adjusted based on the INR. Patients typically have INRs and dose adjustments initially completed on a weekly basis as an outpatient. Once the patient has multiple INRs in their desired range, monitoring is titrated to much longer intervals (i.e. multiple weeks to a month or longer).<sup>31</sup> It is not uncommon for patients to have their dose changed throughout the year or for patients to be on different doses different days of the week (i.e. 5 mg by mouth daily on Monday, Wednesday, Friday and 10 mg by mouth daily on Sunday, Tuesday, Thursday, Saturday).

Warfarin comes in nine different tablet strengths.<sup>32</sup> Brand and generic products are color coded to allow for visual identification of the strength by the patient, pharmacy technician, and pharmacist. The 1 mg tablet will always be pink in color and the 10 mg tablet will be white, for example. See **Table 5** for all of the available strengths and associated colors.<sup>32</sup>

Certain foods and beverages can have clinically significant interactions with warfarin and affect the dose needed.<sup>32</sup> High vitamin K consumption, like eating green leafy vegetables and certain vegetable oils, can cause the INR to decrease, resulting in an increase in warfarin dose. The best

practice for patients taking warfarin is to eat a well-balanced and consistent diet.<sup>30,32</sup> Suddenly eliminating these foods from the diet is not recommended. Instead, patients should continue to eat the foods they desire, and a dose adjustment of warfarin can be made if needed. See **Table 6** for a sample of high content vitamin K foods.<sup>30</sup> Please note, this table is not all-inclusive, just a sample of selected foods. A more in depth listing of vitamin K content in select foods can be found at <http://www.clotcare.com/include/vitaminkcontent.pdf>. Similar to dietary vitamin K consumption, alcohol consumption can affect how the body metabolizes warfarin.<sup>30</sup> Alcoholic drinks should be limited to occasional use, and no more than 1 to 2 servings at a time.<sup>30</sup>

**Table 5. Warfarin Tablet Strengths and Colors<sup>32</sup>**

<i>Strength</i>	<i>Color</i>
1 mg	Pink
2 mg	Lavender
2.5 mg	Green
3 mg	Tan
4 mg	Blue
5 mg	Peach
6 mg	Teal
7.5 mg	Yellow
10 mg	White

**Table 6. Foods High in Vitamin K<sup>30</sup>**

Broccoli	Lettuce
Cabbage	Mayonnaise
Collard Greens	Spinach
Kale	Vegetable Oil

Warfarin is also associated with numerous drug-drug interactions.<sup>32</sup> With certain concomitant medication use, it is recommended the INR be monitored more closely due to altered warfarin exposure. Drug-drug interactions that result in a general increased bleeding risk include other anticoagulants, antiplatelet agents, nonsteroidal anti-inflammatory medications (NSAIDs) and aspirin.<sup>32</sup> Antibiotics and antifungal medications can have variable effects on warfarin; some can cause significant elevations in the INR and others cause a decrease in the INR resulting in an increased risk for VTE.<sup>30</sup>

Although diet, alcohol, and other medications can affect a patient's optimal dose of warfarin, another factor that can influence a response is the patient's genetics. Specifically, variations in the 2 genes, CYP2C9 and VKORC1, play a key role.<sup>33</sup> In 2010, the FDA updated warfarin's package insert to give information on these mutations. This can assist clinicians in selecting an appropriate starting dose for the drug. At this time, the FDA does not require that genetic testing be completed prior to initiation of this therapy.<sup>32</sup>

Some of the other possible adverse reactions to warfarin are gangrene, "purple toes" syndrome, hair loss, itching, rash, weakness, and nausea.<sup>32</sup>

### ***Direct Thrombin Inhibitors and Factor Xa Inhibitors***

Dabigatran (Pradaxa), rivaroxaban (Xarelto), and apixaban (Eliquis) are the newest anticoagulants approved by the FDA in the U.S. Each of these drugs prevents blood clots by inhibiting one clotting factor. These new agents offer several advantages over warfarin. They produce a predictable effect, that when given in fixed doses, drug interactions are significantly less common, dietary interactions are nonexistent, and the routine laboratory monitoring (i.e. PT/INR) is not necessary. Furthermore, these agents are as efficacious as warfarin at preventing new or recurrent VTEs and strokes in patients with AF.<sup>34,35,36,37,38,39</sup>

Dabigatran, a direct thrombin inhibitor (DTI), is approved for patients with AF to reduce the risk of a stroke.<sup>40</sup> The medication is usually ordered 150 mg by mouth twice daily. If the patient has decreased kidney function, the dose may be reduced to 75 mg by mouth twice daily.<sup>41</sup> The capsules should NOT be opened, crushed, or broken prior to ingesting.<sup>40</sup> Doing so can result in the patient receiving more of the drug than intended and could lead to serious bleeding problems. These capsules are also sensitive to moisture in the air. This medication should be dispensed and stored in the bottles or unit dose blister packs from the manufacturer. Patients should be instructed to discard any remaining capsules 120 days (4 months) after opening the original bottle.<sup>41</sup> The most commonly reported side effect with this medication is dyspepsia (heart burn/indigestion).<sup>41</sup> Other possible side effects are rash, itching, and abnormal liver enzymes.<sup>41</sup>

Rivaroxaban was the first oral factor Xa inhibitor to the market in the U.S. This agent has multiple approved indications: reducing the risk of stroke in AF patients, DVT and PE treatment and secondary preventions, and specifically, preventing VTE events in patients recently having knee and hip replacements.<sup>42</sup> Depending upon the indication, the total dose requirements range from 10 to 30 mg by mouth daily.<sup>43</sup> Patients taking 10 mg by mouth one time per day may do so without regard to a meal. It is suggested all other doses be administered with food.<sup>42,43</sup> The manufacturer reports the 15 mg and 20 mg tablets may be crushed and mixed with applesauce to help in dose administration to the patient.<sup>42</sup> Some side effects for this medication include swelling, headache, dizziness, pain in the arms and/or legs, and itching.<sup>43</sup>

Apixaban is classified as an oral factor Xa inhibitor and is approved for patients with AF to prevent stroke and sys-

#### ***Test Your Knowledge #3:***

Pair the correct warfarin tablet strength (number) with the associated color (letter).

<b>Strength</b>	<b>Color</b>
1. ____ 1 mg	A. Lavender
2. ____ 2 mg	B. Tan
3. ____ 2.5 mg	C. Peach
4. ____ 3 mg	D. Pink
5. ____ 4 mg	E. White
6. ____ 5 mg	F. Yellow
7. ____ 6 mg	G. Green
8. ____ 7.5 mg	H. Teal
9. ____ 10 mg	I. Blue

*Answers on page 24.*



temic VTE events.<sup>44</sup> The standard dose is 5 mg by mouth twice daily. Certain patients (age 80 years or older, body weight 60 kg or less, and/or abnormal kidney function) may have the dose lowered to 2.5 mg by mouth twice daily.<sup>45</sup> This medication can be given with or without food, whichever the patient prefers.<sup>44,45</sup> The patient should be encouraged to take the medication 12 hours apart, or as close to that interval as possible. Apixaban may have a slight benefit for patients requiring anticoagulation who also have recurrent gastrointestinal (stomach) bleeds.<sup>34</sup> A few side effects for apixaban include nausea, low blood pressure, rash, and wound secretions.<sup>45</sup>

## Injectable Medications

Heparin, low molecular weight heparin (LMWH), fondaparinux, desirudin, bivalirudin, and argatroban are all medications given via subcutaneous (under the skin) or intravenous (IV) administration. Like the oral anticoagulants, many differ in pharmacokinetic properties or FDA approved indications. Nevertheless, the ultimate goal of therapy remains the same, to either prevent or treat VTE events.

### Heparin

In 1916, it was discovered that heparin had anticoagulant properties; making heparin the oldest anticoagulant still used today.<sup>46</sup> Heparin is used in patients undergoing PCI, for VTE prophylaxis (prevention), and for the treatment of VTE. Heparin is also commonly used in dialysis patients to maintain implanted port patency, to flush IV lines in the hospital, and has a place in treatment in parenteral nutrition therapy.<sup>47</sup> Heparin dosing varies. For certain indications the dose is fixed (i.e. 5,000 units subcutaneously three times daily for VTE prevention). For others, heparin dosing can fluctuate and can be titrated to reach the desired effect.<sup>47,48</sup>

The laboratory test used to measure the effectiveness of heparin (and other medications) is known as the activated partial thromboplastin time (aPTT).<sup>47</sup> This blood test will measure how long it takes the blood sample to form a blood clot.<sup>49</sup> For someone not on heparin, the normal range is usually 25-35 seconds.<sup>49</sup> Small variations in the range can occur between laboratories. Depending on the dose of heparin, the desired aPTT can be 1.5 to 2.5 times the normal range.<sup>47,48</sup>

Heparin is the anticoagulant of choice for use in the pediatric patient population. Dosing differs in children as compared to adults, as pediatric patients have different physiological characteristics which influence the activity of heparin.<sup>50</sup> When selecting a product for use in this population, the use of preservative-free products is essential in neonates and infants.<sup>48</sup> The preservative benzyl alcohol has been found to cause serious adverse events and deaths in neonates. The FDA also notes that premature and low-birth weight infants may be more likely to develop these complications.<sup>51</sup>

Numerous commercial preparations are available for this drug – such as vials, IV bags, and prefilled syringes. Extra caution should be exercised when selecting the product from the dispensing area due to the large number of available products and strengths. The strength is listed in terms of units/mL (i.e. 500 units/mL). See **Table 7** (page 10) for a summary of the dosage forms available for heparin and the other anticoagulants discussed in this module.

Some possible side effects associated with heparin use include hair loss, fever, chills, constipation, and osteoporosis. In addition, injection site reactions such as irritation, pain, and bruising have been reported.<sup>47,48</sup>

### Low Molecular Weight Heparins

Low molecular weight heparins (LMWHs) have moved to the forefront and replaced the routine use of heparin for prevention and treatment of VTE events, mainly due to improved (predictable) drug properties and ease of use.<sup>31</sup> As with all forms of anticoagulant therapy, correct dosing of LMWHs is essential for achieving the optimal balance between effectiveness and bleeding risk. However, as a result of the differences between LMWHs, equivalent doses within the class have not been established; thus, substituting one product for another is not recommended.<sup>52</sup>

#### *Enoxaparin (Lovenox)*

Of the available LMWHs, enoxaparin has the broadest range of FDA approved indications and is used most often.<sup>53,54</sup> Another advantage of enoxaparin over other LMWHs is this medication has been studied in two additional populations: pediatric and pregnant patients.<sup>54</sup> Enoxaparin has fixed dosing for certain indications (i.e. 40 mg subcutaneously daily for VTE prophylaxis) and

<b>Table 7. Anticoagulants Available in the United States<sup>32,41,43,45,47,54,55,57,58,62,63,65</sup></b>					
Generic Name	Brand Name	Route of Administration	Dosage Forms	Commercial Preparation	Generic Availability*
Warfarin	Coumadin Jantoven	Oral	Tablet	1, 2, 2.5, 3, 4, 5, 6, 7.5, 10 mg	Yes
Dabigatran	Pradaxa	Oral	Capsules	75, 150 mg	No
Rivaroxaban	Xarelto	Oral	Tablet	10, 15, 20 mg	No
Apixaban	Eliquis	Oral	Tablet	2.5, 5 mg	No
Enoxaparin	Lovenox	Subcutaneously, Intravenously	Injectable Solution	30, 40, 60, 80, 100, 120, 150 mg pre- filled syringes  300 mg/3mL vial	Yes
Dalteparin	Fragmin	Subcutaneously, Intravenously	Injectable Solution	2,500 IU (0.2 mL), 5,000 IU (0.2 mL), 7,500 IU (0.3 mL), 10,000 IU (0.4, 1 mL), 12,500 IU (0.5 mL), 15,000 IU (0.6 mL), 18,000 IU (0.72 mL) prefilled syringes  10,000 IU/1 mL single-dose graduated syringe  95,000 IU/9.5 mL, 95,000 IU/3.8 mL vials	No
Tinzaparin	Innohep	Subcutaneously, Intravenously	Injectable Solution	20,000 IU/mL (2 mL) vial	No
Fondaparinux	Arixtra	Subcutaneously	Injectable Solution	2.5, 5, 7.5, 10 mg prefilled syringes	Yes
Heparin	Hep Flush-10	Subcutaneously, Intravenously	Injectable Solution	1 unit/mL (3 mL), 10 units/mL (1, 3, 5, 10 mL), 100 units/mL (1, 3, 5 mL), 1,000 units (500 mL), 2,000 units (1000 mL), 25,000 units (250 mL, 500 mL), 1,000 units/mL (1, 2, 10, 30 mL), 2,500 units/mL (10 mL), 5,000 units/ mL (1 mL, 10 mL), 5,000 units/0.5 mL (0.5 mL), 10,000 units/mL (1 mL, 4 mL, 5 mL), 20,000 units/mL (1 mL)  Many concentrations available in prefilled syringes, bags, and/ or vials	Yes
Bivalirudin	Angiomax	Intravenously	Injectable Solution (once reconstituted)	250 mg vials	No
Desirudin	Iprivask	Subcutaneously	Injectable Solution	15 mg vial	No
Argatroban		Intravenously	Injectable Solution	125 mg/125 mL bag (125 mL), 100 mg/ mL (2.5 mL) vial	Yes

\*As of November 1, 2013  
IU=International unit

also has dosing recommendations which take into account the patient's body weight (i.e. 1 mg/kg subcutaneously twice daily for DVT/PE treatment).<sup>54</sup> Dosing adjustments are recommended for patients with kidney impairment and for obese patients.<sup>53</sup> This drug is administered intravenously and subcutaneously. Patients can be taught how to give subcutaneous injections of enoxaparin at home. This is usually done before and/or after surgical procedures.<sup>54</sup> A counseling point for patients is; when injecting, in order to avoid loss of drug from the 30 mg and 40 mg prefilled syringes, do not expel the air bubble from the syringe prior to injection.<sup>54</sup> Some possible side effects associated with enoxaparin use include confusion, nausea, diarrhea, and fever. In addition, injection site reactions such as irritation, pain, bruising, and redness have also been reported in the literature.<sup>54</sup>

### *Dalteparin (Fragmin)*

FDA approved indications for dalteparin are fewer in number than enoxaparin; however, it offers expanded coverage for cancer patients. Dalteparin has been approved for the long term secondary prevention of VTE in patients with prior VTE and a history of cancer.<sup>55</sup> Dalteparin also has fixed dosing for certain indications (i.e. 2,500 units subcutaneously daily for DVT prophylaxis) and also has dosing recommendations taking into account the patient's body weight (i.e. 200 units/kg subcutaneously daily for VTE extended treatment in cancer patients).<sup>55,56</sup> Dalteparin should not be used in certain patients with kidney or liver disease.<sup>56</sup> Some possible side effects associated with dalteparin use include injection site reactions such as irritation, pain, and bruising.<sup>55</sup>

### *Tinzaparin (Innohep)*

Of the three LMWHs, tinzaparin has the fewest FDA approved indications.<sup>57</sup> A labeling revision in 2008 created age criterion. Patients 90 years of age or older are not to use this agent under any circumstance.<sup>52</sup> The smaller number of indications and the maximum age criteria outlined by the drug manufacturer may explain why it is used infrequently in the U.S. today.<sup>52</sup> However, when used, tinzaparin can be given intravenously or subcutaneously. Also, dosing may be fixed or variable depending upon patient specific characteristics.<sup>57</sup> Some of the reported side effects for this medication include: chest pain; rash; constipation; vomiting; and irritation, pain, and redness at the injection site.<sup>57</sup>

### **Factor Xa Inhibitors**

Fondaparinux (Arixtra) is the only injectable factor Xa inhibitor available on the market. This product's dosing is based on weight, but will always be 2.5, 5, 7.5, or 10 mg subcutaneously daily.<sup>58</sup> This product is used for many approved indications. However, fondaparinux's unique use is in patients with an allergic reaction to heparin or LMWH, called heparin induced thrombocytopenia (HIT).<sup>58,59</sup> This, however, is not an FDA-approved indication. Similar to enoxaparin, due to the ease of use and prefilled syringes, this product can be used at home by patients to prevent or treat VTE events.<sup>60</sup> Possible side effects for fondaparinux are fever, swelling, rash, insomnia, dyspepsia, in addition to injection site reactions like pain, bruising, and redness.<sup>58</sup>

### **Direct Thrombin Inhibitors (DTI)**

Three medications, desirudin (Iprivask), bivalirudin (Angiomax), and argatroban encompass the injectable DTI class. Desirudin and bivalirudin are derivatives of another medication called hirudin.<sup>61</sup> Desirudin is only to be given as a subcutaneous injection for patients needing prophylaxis of DVT due to hip replacement surgery.<sup>62</sup> The recommended dosing regimen is 15 mg subcutaneously every 12 hours.<sup>62</sup> Desirudin is commercially available in a unique manner. The components supplied by the manufacturer include a tablet in a vial and a premeasured diluent in a syringe. Directions for dilution are as follows: attach provided syringe containing diluent to adapter on vial. Slowly push plunger down to transfer entire contents of syringe into vial. Do not remove syringe from vial adapter. Gently swirl solution; the round tablet in vial will dissolve within 10 seconds.<sup>62</sup> Possible side effects for desirudin include injection site mass, wound secretion, dizziness, fever, healing impairment, leg swelling, and vomiting.<sup>62</sup>

Compared to desirudin, bivalirudin offers a few advantages. The onset of action is much quicker with bivalirudin. It has a shorter half-life (25 minutes versus 80 minutes). Also, bivalirudin is predominately not removed from the body by the kidneys.<sup>61</sup> These properties make this drug ideal for patients undergoing a PCI. Initially, an IV bolus of 0.75 mg/kg is given, followed by a continuous infusion of 1.75 mg/kg/hr.<sup>63</sup> Although not an approved indication, clinicians utilize this medication for treating patients with HIT.<sup>63</sup> Bivalirudin is solely administered by IV infusion and the dose may be adjusted based on aPTT

findings.<sup>63</sup> Patients receiving bivalirudin may be subject to any of the following side effects: low blood pressure, headache, pain, nausea, low heart rate, nervousness, and pain at injection site.<sup>63</sup>

Argatroban is a DTI administered by continuous IV infusion and is approved for patients with HIT to prevent thrombosis, including patients undergoing PCI with a high risk of HIT. Dosing is initiated at 2 mcg/kg/min, with subsequent dose adjustments determined by the aPTT.<sup>64</sup> The target range aPTT is 1.5 to 3 times the patient baseline aPTT. The recommended maximum dose should not exceed 10 mcg/kg/min.<sup>65</sup> Argatroban is commercially available in a prefilled bag and as a vial to be used for manual dilution. A few possible side effects for this medication include chest pain, fever, headache, cough, trouble breathing, and pain at the injection site.<sup>65</sup> See **Table 7** (page 10) for additional details on available dosage forms.

antidotes available for this situation. Some of the other medications discussed previously do not have specific agents to neutralize them. Some anticoagulant class effects may be reversed with certain blood products and/or medications not specifically indicated to do so.<sup>25</sup>

The newer anticoagulants have been available for a shorter length of time; therefore, data regarding possible reversal strategies are still evolving and lack national consensus guidelines at this point in time.<sup>25,66</sup> Many clinicians are forced to use professional judgment and look at off label use of some agents to treat patients requiring immediate reversal of anticoagulation. To see if an anticoagulant has a suggested antidote, see **Table 8**.<sup>25,66,67</sup> Note, the continuous IV infusion products desirudin, bivalirudin, and argatroban do not need reversal with a specific antidote due to certain pharmacokinetic properties.<sup>68</sup> The treatment of choice is stopping the infusion of these select anticoagulants and using supportive measures if necessary.<sup>67,68</sup>

**Test Your Knowledge #4:**

Pair the number (description) with the letter (medication).

- | Description  | Medication      |
|--|-----------------|
| 1. _____ The only injectable factor Xa inhibitor available             | A. Heparin      |
| 2. _____ A direct thrombin inhibitor; dosing initiated at 2 mcg/kg/min | B. Enoxaparin   |
| 3. _____ A low molecular weight heparin                                | C. Fondaparinux |
| 4. _____ Anticoagulant of choice for pediatric patients                | D. Bivalirudin  |
| 5. _____ A direct thrombin inhibitor; a derivative of hirudin          | E. Argatroban   |

*Answers on page 24.*

**REVERSAL STRATEGIES**

In the patient taking anticoagulants with a case of severe bleeding, or when a patient needs to undergo an emergency surgery, it may be useful to reverse the anticoagulant effect. The older anticoagulants (i.e. warfarin and heparin) have

**Vitamin K**

Vitamin K, also referred to as phytonadione (Mephyton), is a vitamin used to reverse the effects of vitamin K antagonists.<sup>69</sup> Oral administration of this product is preferred over all other routes of administration. However, the manufacturer states that subcutaneous injection is the preferred injectable route. Intramuscular injection (IM) should be avoided due to the risk of hematoma formation. Intravenous injection should be restricted for emergency use only.<sup>70</sup> There are not definitive guidelines as to how much (i.e. dose) and when (i.e. at what INR) to begin administering vitamin K;<sup>69</sup> as holding anticoagula-

**Table 8. Agents for Reversal of Select Anticoagulants<sup>25,66,67</sup>**

<i>Anticoagulant</i>	<i>Reversal Agent</i>
Fondaparinux	Recombinant Factor VIIa*
Heparin	Protamine
Low Molecular Weight Heparins	Protamine
Oral Direct Thrombin Inhibitors	None
Oral Factor Xa Inhibitors	Prothrombin Complex Concentrate (Kcentra)*
Warfarin	Vitamin K, Prothrombin Complex Concentrate (Kcentra)
* Experimental Treatment	

tion therapy is also a potential reversal option for those not bleeding. If phytonadione is given by IV infusion, it should be administered slowly.<sup>69</sup> Appropriate dosing ranges from 1 mg to 10 mg for this product.<sup>69</sup>

### *Protamine*

When protamine is given to reverse the effects of heparin, the neutralization begins to occur about 5 minutes after administration.<sup>71</sup> The protamine dose is determined by the amount of heparin received. One (1) mg of protamine is needed for every ~100 units of heparin received with a maximum dose of 50 mg of protamine.<sup>71</sup> This product can also be used for the reversal of LMWHs; however, the effect is incomplete and not as predictable.<sup>72</sup> When given, it is administered by slow IV infusion, as too rapid of an infusion can cause blood pressure issues.<sup>71</sup>

### *Prothrombin Complex Concentrate*

Prothrombin complex concentrate (Kcentra) is a blood derivative product indicated in patients on warfarin with acute major bleeding.<sup>73</sup> The dosing is individualized based on current pre-dose INR and ranges from 25 to 50 units/kg intravenously.<sup>73,74</sup> The maximum dose allowed is 5,000 units.<sup>74</sup> The manufacturer also states vitamin K needs to be given concurrently and repeat dosing of the product is not recommended.<sup>73</sup> After the completion of the infusion, a rapid and significant INR decline can be expected in about 10 minutes.<sup>73,74</sup> Prothrombin complex concentrate (Kcentra) is also being studied as a potential reversal agent for some of the newer oral anticoagulants. If this product is currently given for this purpose, this would be an off-label use and is still investigational. Although no large studies have been conducted, smaller studies suggest this product could be beneficial in patients who need urgent reversal of oral factor Xa inhibitors (i.e. rivoraxaban and apixaban).<sup>25</sup>

Another prothrombin complex concentrate (Feiba NF) is currently available in the U.S. as a potential reversal agent. This blood derivative product is indicated for the control of bleeding in patients with inherited bleeding disorders.<sup>75</sup> This product is typically ordered 50 to 100 units/kg intravenously per dose. Total number of doses and the duration of treatment depends on the location and severity of the bleeding and other patient factors.<sup>76</sup> When administering, the maximum infusion rate must not exceed 2 units/kg/minute.<sup>75</sup>

### *Recombinant Factor VIIa*

The last reversal agent to be covered by this article is recombinant factor VIIa (NovoSeven RT). This product is indicated in patients with inherited bleeding disorders with acute bleeding episodes and those needing surgical interventions.<sup>77</sup> Dosing and frequency for this product ranges greatly depending upon indication and other patient specific factors, but can range from 10 to 120 mcg/kg intravenously.<sup>78</sup> When utilized, this product can be administered for several days in duration.<sup>78</sup>

#### ***Test Your Knowledge #5:***

List the recommended reversal agent with the appropriate anticoagulant from the choices below. Each choice may only be used once.

1. Heparin; \_\_\_\_\_
2. Oral Factor Xa Inhibitors; \_\_\_\_\_
3. Fondaparinux; \_\_\_\_\_

Choices:

Protamine  
Prothrombin Complex Concentrate  
Recombinant Factor VIIa

*Answers on page 24.*

## **PATIENT RESOURCES**

A number of resources are available to assist patients; a few of those available nationally are listed in **Table 9** (page 14). If a patient is unable or struggles with paying for their anticoagulant prescription, some of the manufacturers offer financial assistance programs. Although not included in the table, they are another resource to which patients can be directed.

## **CONCLUSION**

Anticoagulants are used by a large number of patients for a wide array of diseases and conditions. With three new oral anticoagulants approved for use in the U.S. in the last three years, prescribers have even greater options for patients looking for maintenance therapy as warfarin is no longer the only long term option. As always with new therapies, the

**Table 9. Resources for Patients**

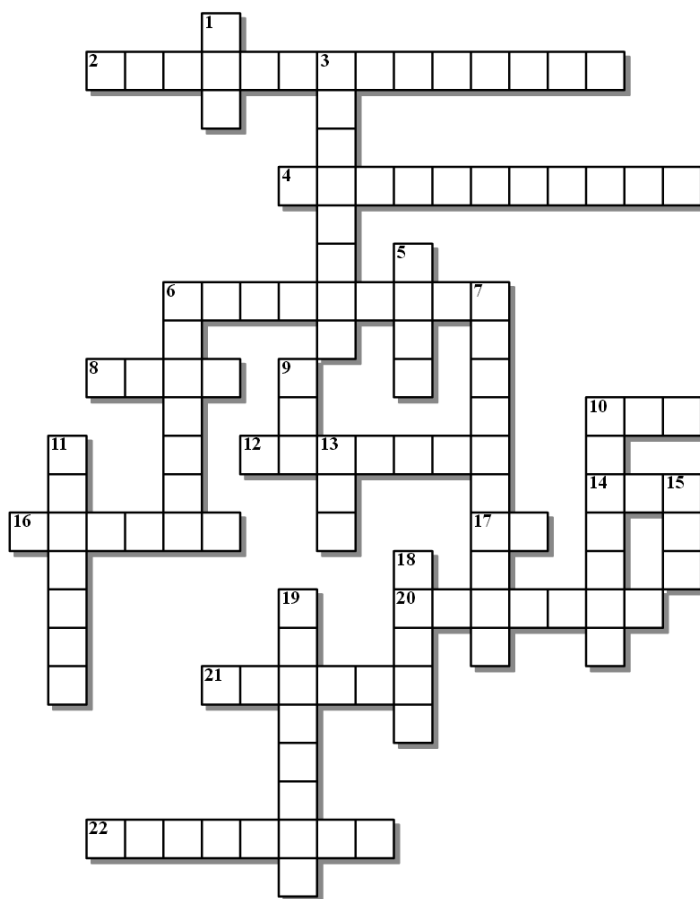
Agency for Healthcare Research and Quality <a href="http://www.healthcare411.ahrq.gov/videocast.aspx?id=555">http://www.healthcare411.ahrq.gov/videocast.aspx?id=555</a>
American Heart Association <a href="http://www.heart.org/HEARTORG/">http://www.heart.org/HEARTORG/</a>
American Stroke Association <a href="http://www.strokeassociation.org/STROKEORG/">http://www.strokeassociation.org/STROKEORG/</a>
Centers for Disease Control and Prevention <a href="http://www.cdc.gov/ncbddd/dvt/index.html">http://www.cdc.gov/ncbddd/dvt/index.html</a> <a href="http://www.cdc.gov/stroke/">http://www.cdc.gov/stroke/</a>
ClotCare Online Resource <a href="http://www.clotcare.com">http://www.clotcare.com</a>
Clot Connect <a href="http://www.clotconnect.org/patients">http://www.clotconnect.org/patients</a>
National Blood Clot Alliance <a href="http://www.stoptheclot.org/">http://www.stoptheclot.org/</a>
National Heart, Lung, and Blood Institute <a href="http://www.nhlbi.nih.gov/health/health-topics/topics/dvt/">http://www.nhlbi.nih.gov/health/health-topics/topics/dvt/</a>
North American Thrombosis Forum <a href="http://www.natfonline.org/patients/">http://www.natfonline.org/patients/</a>

out of pocket costs and co-payments are likely to be more expensive for patients; however, the many advantages and flexibility of these agents are driving a large number of patients to switch or consider these medications.

It is important to recognize the potential impact the pharmacy technician can have on patients utilizing anticoagulants. Whether providing an educational resource to the patient, ensuring proper dispensing following an order/prescription for an agent, or assisting the pharmacist in ensuring the goals of medication therapy are met for each patient. Pharmacy technicians are helping to prevent errors.

Finally, the goals of medication therapy with anticoagulants are as follows; select the best anticoagulant for each patient taking into account patient preferences and medical history, use the appropriate dose of each anticoagulant to ensure effectiveness, and minimize the potential risk(s) for adverse drug events and errors to protect the patient from a safety standpoint. Doing so will provide the best care and quality of life for the patient; the ultimate goal of all medication therapies.

**Test Your Knowledge #6**



**Across:**

- 2 One of two possible routes of administration for tinzaparin.
- 4 The generic name for the first oral factor Xa inhibitor available in the United States.
- 6 The drug given to reverse the effects of heparin.
- 8 The preferred route of administration for vitamin K.
- 10 The abbreviation for the condition used to describe an allergic reaction to heparin.
- 12 The brand name for a blood derivative product indicated in patients with acute major bleeding taking warfarin.
- 14 A procedure to open narrowed heart arteries.
- 16 One of two valves that when replaced require the use of an anticoagulant.
- 17 An abbreviation for a heart arrhythmia characterized by rapid and disorganized contraction.
- 20 The brand name for a medication where the standard dose is 5 mg by mouth twice daily.
- 21 A medical emergency defined as the rapid loss of brain function.
- 22 The most severe side effect of anticoagulants.

**Down:**

- 1 A sock-like device used to prevent the formation of a DVT in the legs.
- 3 The brand name for bivalirudin.
- 5 Warfarin comes in \_\_\_ different tablet strengths.
- 6 The brand name for dabigatran.
- 7 The generic name for the LMWH that has the broadest range of FDA approved indications.
- 9 The abbreviation for a nonpharmacological filter for patients that can't use conventional therapies to prevent a PE.
- 10 The generic name for the anticoagulant discovered in 1916.
- 11 The brand name for fondaparinux.
- 13 A test used to diagnose atrial fibrillation.
- 15 The laboratory test used to determine the dose of warfarin.
- 18 CYP2C9 and VKORC1 are two \_\_\_ that can influence a response to warfarin.
- 19 The most commonly prescribed outpatient anticoagulant.

Answers on page 24.

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ANSWER KEY: TEST YOUR KNOWLEDGE EXERCISES

**Exercise #1:** Cancer, Inherited Thrombophilic Disorders, Obesity, Oral Contraceptive/Hormone Replacement Therapy Use, Pregnancy, Prolonged Immobilization, Surgery, Trauma

**Exercise #2:** Graduated Compression Stockings, Inferior Vena Cava Filter, Intermittent Pneumatic Compression Devices

**Exercise #3:** 1D; 2A; 3G; 4B; 5I; 6C; 7H; 8F; 9E

**Exercise #4:** 1C; 2E; 3B; 4A; 5D

**Exercise #5:** 1. Protamine; 2. Prothrombin Complex Concentrate; 3. Recombinant Factor VIIa

**Exercise #6:**

