The Impact of Direct Oral Anticoagulants in the Managed Care Environment

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Educational Objectives

At the completion of this activity, the participant will be able to:

1. Recall the prevalence, incidence, and economic impact of venous thromboembolism (VTE) and atrial fibrillation (AF) on patients with these conditions.
2. Outline the effects that nonadherence has on the health, treatment effectiveness, quality of life, and healthcare-associated cost for patients with VTE and/or AF.
3. Discuss clinical trial data comparing the safety and efficacy of new oral anticoagulants with warfarin.
4. Express clinical data that determines the cost-efficacy of new direct oral anticoagulants compared with warfarin when taking long-term treatment, monitoring, and risk prevention into account.
5. Recognize the impact of appropriate prophylactic treatment on VTE outcomes.

Target audience: The intended audience for this activity consists of physicians and pharmacists practicing within accountable care organizations (ACOs), Pharmacy and Therapeutics (P&T) Committee members, pharmacy directors, and managed care professionals.
Type of activity: Knowledge
Release date: December 12, 2015
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Medium: Print with Internet-based posttest, evaluation, and request for credit
Estimated time to complete activity: 2.0 hours
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Impact of Thromboembolic Events: Morbidity, Mortality, and Cost

Thrombosis refers to abnormal, potentially life-threatening blood clots that form in the vein, artery, or heart. When it occurs in a vein, it is known as a deep vein thrombosis (DVT), and can break off and cause a pulmonary embolism (PE). DVT and PE compose venous thromboembolism (VTE). Atrial fibrillation (AF) can cause clots in the atrium (usually the atrial appendage), which can break off and cause a stroke or systemic embolism.[1] Together, VTE and AF are among the leading causes of morbidity and mortality in the United States due to their long term complications.[2-4] They are also a source of significant cost and economic burden; however, the emergence of accountable care organizations (ACOs) and their shift from a fee-for-service model, toward a population health model, may lead to improvements in care and decreased costs. In this drive to decrease overall healthcare costs and reduce hospitalizations, it is important to focus on more effective management of not only the traditional agents used, such as warfarin, but also the newer anticoagulants that are altering the treatment landscape.[5,6]

Prevalence and Incidence of Venous Thromboembolism

VTE is a disease process in which blood clots form; it often occurs in response to an acute and short-lasting risk. It includes DVT, in which the clot usually occurs in the leg and sometimes in the upper extremity, as well as PE,[2,7,8] which typically happens when a DVT breaks free and moves through the bloodstream to the lungs where it can block the arteries that supply blood to the lungs.[2,7] Since there are no formal national US surveillance systems for VTE, the true incidence of VTE is not well-specified, and it is suspected that occurrences are underreported.[2,7] However, it is estimated that between 900,000 and 2 million Americans suffer from VTE each year.[3] Clinical administrative databases and hospital records estimate the national incidence of VTE to be between 300,000 to 600,000 cases each year, or 1 to 2 per 1000 of the US population.[5] The incidence increases strongly with age and varies greatly by race. Those aged between 15 to 44 years have an estimated incidence rate of 1.5 per 1000 compared with 1.9 per 1000 for those aged 45 to 79 years, and 5 to 6 per 1000 for those 80 years or older. The incidence is higher among blacks (reported to be as high as 1.4 per 1000) compared with whites (1.2 per 1000), and lowest among Asians (0.3 per 1000).[7]

VTE: morbidity and mortality. VTE is associated with high morbidity and mortality: 10% to 30% of patients with VTE die within 1 month of the diagnosis. An estimated 30,000 to 200,000 deaths due to VTE each year are attributed to PE alone,[3] and sudden death is the first symptom in 20% to 25% of cases. Since many cases are likely undiscovered or undiagnosed, PE is considered a "silent disease,"[7] and as such, community-based epidemiological studies suggest that the annual death rate may be closer to 82,800.[9] Unfortunately, however, the majority of these deaths result from a failure in diagnosis or a failure to prophylax at-risk hospitalized patients.[10]

Serious long-term complications of VTE include increased risks of recurrent thromboembolism and chronic morbidity from conditions such as post thrombotic syndrome (PTS), chronic venous insufficiency, and chronic thromboembolic pulmonary hypertension. For many patients, VTE will not be a 1-time event. A long-term follow-up study of 1719 patients found that the risk of recurrence was greatest 6 to 12 months after the initial event, with the overall cumulative percentage of VTE recurrence at 10% at 180 days and 13% at 1 year. Even with a standard course of anticoagulant therapy, approximately one-third of patients with VTE had a recurrence within 10 years after the initial event.[7,11] PTS is the most common complication of DVT, and is a potentially debilitating condition that develops in 20% to 40% of patients, typically manifesting within 2 years of the acute DVT.[10,12,13] The economic burden of PTS in the United States has been estimated as high as $200 million annually,[14] and annualized median total costs for PTS in DVT patients with or without (±) PE are estimated at $20,569, compared with $15,843 for patients with DVT ± PE, without PTS.[15] Worsening of PTS scores have been associated with declining physical health status, decreased productivity, and other quality of life measures, indicating that the morbidity resulting from DVT may be chronic.[12,13]

Hospital-associated VTE. Although VTE affects both hospitalized and nonhospitalized patients, hospitalization is by far one of the most common risk factors for VTE, and PE remains the most common preventable cause of death in the hospital.[2,3] Based on the National Hospital Discharge Survey (2007-2009), the CDC estimated that an average of 547,596 hospitalizations with VTE occurred each year among those 18 years or older in the United States: 348,558 with DVT, 277,549 with PE, and 78,511 with DVT and PE.[2] Age-based hospitalization rates for VTE, DVT, and PE increased substantially with age (see **Figure 1**[2]).[2] Five percent of patients with a primary diagnosis of DVT or PE and 14% for secondary diagnosis were readmitted within 1 year.[16]

The risk of hospital-associated VTE is significant among all populations of hospitalized patients: according to venographic rates, 10% to 26% in medically ill patients; 15% to 40% for patients undergoing neurosurgery, major gynecological or urological surgery, or general surgery; 40% to 60% for patients undergoing hip or knee surgery; 40% to 80% for major trauma patients; and 60% to 80% for patients with spinal cord injury.[3] Overall, more than half of the 2 million VTE cases each year result from a prolonged or post surgical hospital stay.[3] However, it is important to note that this does not imply that the VTE always occurs in the hospital setting, especially since approximately 74% of patients developing VTE do so in an outpatient setting. From those, 23% had undergone surgery and 37% had been hospitalized within the past 3 months, but 30% of those patients did not have a recent

hospitalization, recent surgery, active malignancy, recent infection, or previously documented episode of VTE. In fact, patients who presented with VTE in the outpatient setting tended to be younger (33% aged <55 years, 66% aged <74 years; P <.001) and were less likely to have had recent heart failure, cardiac procedure, or infection (P <.001).[17]

VTE: economic impact. Regardless of the setting, the economic impact of VTE is substantial. Recent estimates place the national cost of VTE between $13.3 billion and $69.3 billion, with preventable costs representing $4.5 to $39.3 billion (estimates in 2011 US$). In a recent study estimating the economic costs of VTE in 49,948 hospitalized nonsurgical patients aged over 40 years, the adjusted mean total health cost over 180 days was $17,848 higher, per patient, for those with a VTE diagnosis at admission versus those without VTE ($47,416 vs $29,568; P <.001), and $51,863 higher for those with a postdischarge diagnosis of VTE compared with those without ($74,136 vs $22,273; P <.001).[18]

This cost is not just incurred in the initial diagnosis and treatment of VTE. It is ongoing in the recurrences and long-term complications of VTE. In a retrospective analysis using the Integrated Health Care Information Services National Managed Care Database, the economic burden of VTE was quantified based on direct medical costs and utilization over a 7-year period. In patients with a primary diagnosis of DVT (n = 5348), the cost of readmission was 21% higher (P = .006), at $11,862 per patient, compared with the initial hospitalization cost of $9805. The cost for the initial hospitalization for patients with a primary diagnosis of PE (n = 2984) was $14,146, compared with $14,722 (n = 1119) for the cost of readmission. The length of stay was similar in both instances for PE, but higher for readmission due to DVT.[16]

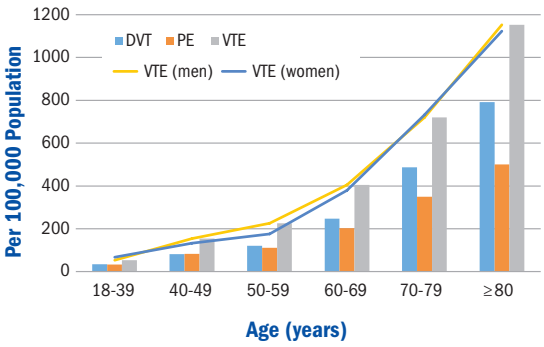
The average total annualized healthcare cost was higher for patients with a primary diagnosis of PE. The majority of these costs, for DVT and PE, were attributed to the cost of the hospitalization facility (see **Figure 2**[16]). The average total annualized healthcare cost was highest for patients presenting with DVT and PE in the secondary diagnosis (n = 64): $27,909.[16]

Importance of VTE Prevention in Hospitalized Patients

The downstream morbidity, mortality, and financial burden associated with VTE highlight why VTE prevention is so important. Unfortunately, rates of prevention are still low in many hospitals, although several studies have shown improved uptake of prophylaxis and/or decreases in preventable VTE.[3,19-22]

CMS, along with the Joint Commission (TJC), recommend the use of VTE prophylaxis as a quality measure for appropriate patients admitted to a hospital or an intensive care unit.[23] Quality measures for VTE prophylaxis and treatment were initially developed by the National Quality Forum and TJC, and are now enforced by TJC and CMS to improve quality in US hospitals.[24] These quality measures are especially relevant because they are

Figure 1. Estimated Average Annual Rate of Hospitalizations with Deep Vein Thrombosis, Pulmonary Embolism, or Venous Thromboembolism (2007-2009)[2]



DVT indicates deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

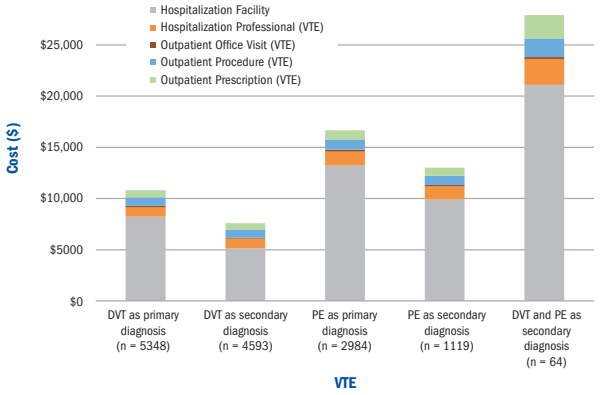
Adapted from Centers for Disease Control and Prevention. Venous thromboembolism in adult hospitalizations—United States, 2007-2009. *MMWR Morb Mortal Wkly Rep*. 2012;61(22):401-404.

tied to the CMS pay-for-performance programs. This means that hospitals have a financial stake in improving the quality of care of patients in the hospital, and the hospitals will bear the increased costs of treating otherwise preventable hospital-acquired conditions, such as hospital-acquired VTE.

As of October 2008, certain preventable hospital-associated DVT and/or PE events, such as VTE events post hip or knee replacement surgery, are no longer reimbursed by CMS.[25] In a study that evaluated the effectiveness of this tactic in improving the quality of healthcare while lowering costs, researchers analyzed 4 groups of Medicare and non-Medicare recipients aged between 60 and 69 years. A model of hierarchical linear regression found that the CMS policy change was independently associated with a 35% reduction in the incidence of hospital-associated PE and DVT in the Medicare patient groups, compared with the non-Medicare patient groups (P = .015).[26]

The 9th edition of the Antithrombotic Therapy and Prevention of Thrombosis (AT9) guidelines by the American College of Chest Physicians (ACCP) recommend the use of pharmacologic prophylaxis, such as low-molecular weight heparin (LMWH) or unfractionated heparin (UFH), in limited patient populations based on the type of surgery being performed, as well as the patient's health status, risk of bleeding, and risk of VTE.[27] Ongoing clinical trials are evaluating the efficacy and safety of pharmacologic novel oral anticoagulant agents rivaroxaban and betrixaban. MARINER is a phase 3, multi-center study evaluating the role of rivaroxaban in reducing the risk of symptomatic DVT and/or PE due to a concurrent medical illness for up to 45 days after hospital discharge. The APEX study is evaluating the extended use of oral

Figure 2. Economic Burden of Hospital Readmission Due to Deep Vein Thrombosis and Pulmonary Embolism as Primary and Secondary Diagnosis[16]



DVT indicates deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

betrixaban as VTE prophylaxis in in-hospital and postdischarge settings in acute medically ill patients. Currently, the only direct oral anticoagulants (DOACs) approved for primary VTE prevention are apixaban and rivaroxaban, which are both approved for VTE prevention after hip and knee replacement surgery.

The significant and preventable burden of hospital-associated VTE presents healthcare professionals and formulary decision makers with a unique challenge to effectively diagnose, prevent, and treat VTE appropriately, thereby reducing mortality rates and unnecessary morbidity and enhancing cost savings for hospitals and managed care organizations. Because ACOs are mostly concerned with containing overall healthcare costs for a patient and maximizing quality, appropriate VTE prevention, treatment, and perioperative management of these patients are ideal areas to focus upon in order to minimize bleeding and thromboembolic events.

Prevalence and Incidence of Atrial Fibrillation

AF is the most common clinically significant type of cardiac arrhythmia[4]; it may be present in as many as 34.5% of patients hospitalized with a cardiac rhythm disturbance.[28] Estimates of AF incidence and prevalence in the United States vary widely. In 2010, the estimated prevalence ranged from approximately 2.7 million to 6.1 million, with women making up approximately 55% of the patient population.[29] Black, Asian, and Hispanic patients have significantly lower adjusted prevalence of AF, but black patients, historically, have been much younger than patients of other races.[29] The lifetime risk for AF is approximately 25% for both men and women 40 years and older—1 in 4 adults aged over 40 years in the United States will experience AF in their lifetime.[30] As with VTE, the prevalence of AF increases with age[4]: over the past 2 decades, the prevalence of AF has increased approximately 5% per year among Medicare patients 65 years and older, growing from about 41.1 per 1000 beneficiaries to 85.5 per 1000 beneficiaries.[29] The National Hospital Discharge Survey/National Center for Health Statistics (1996-2001) found the incidence of AF for patients aged between 15 and 44 years to be 20.6 per 100,000 people per year in men, compared with 6.6 for women. In patients who are 85 years or older, the incidence increased to 1077.4 per 100,000 people per year for men and to 1203.7 for women.[29] A simulation progression model, which uses a health insurance claims database, projected the prevalence of AF to increase to 12.1 million by 2030.[31]

AF: morbidity and mortality. The high prevalence of AF is associated with substantial AF-related morbidity and mortality, with an estimated 99,000 American deaths related to AF on an annual basis.[32] Patients with AF have an almost doubled risk of all-cause mortality over 5 years compared with those without (P <.001), with the risk being even higher in the first 4 months of diagnosis (hazard ratio [HR], 9.6; 95% CI, 8.93-10.32).[33] An adjusted analysis of the Framingham Heart Study associates AF with an increased risk of death in both men (odds ratio [OR], 1.5; 95% CI, 1.2-1.8) and women (OR, 1.9; 95% CI, 1.5-2.2).[34] In 2011, the National Center for Health Statistics reported AF was mentioned on 116,247 death certificates, of which 17,729 (~15 %) showed AF as the underlying cause of death.[29]

In addition to the high rate of mortality, AF is an independent risk factor for ischemic stroke. Patients with AF have a 4- to 5-fold greater risk for stroke than those without AF. As with AF itself, this risk increases with age.[35] AF is responsible for 15% to 20% of all strokes, and for an approximately 5-fold increase in the risk of stroke regardless of whether the patient has paroxysmal or sustained AF.[36-39] However, stroke accounts for only approximately 7% of deaths in AF. The majority of mortality associated with AF results from noncardiovascular death (35.8%), sudden cardiac death (22.25%), and progressive heart failure (15.1%).[29]

AF is also associated with increased morbidity and mortality in patients with other cardiovascular conditions, in patients with noncardiovascular conditions, such as sepsis, and in patients undergoing noncardiac surgery.[29] Other common comorbid chronic conditions associated with AF include hypertension, hyperlipidemia, heart failure, anemia, arthritis, diabetes mellitus, chronic kidney disease, chronic obstructive pulmonary disorder, cataracts, and depression.[40] Additionally, AF has been associated with physical disability and poor subjective health. Patients with AF also have a 2-fold increase in the risk of dementia, kidney dysfunction, and sudden cardiac death. Furthermore, AF shares antecedent risk factors with heart failure and is associated with a 70% increased risk of incident myocardial infarction.[41]

AF: economic impact. The management of AF generates significant healthcare costs. The mean cost per AF-related hospitalization exceeds $8000, with an average length of stay at about 3.5 days.[35] Federal databases attribute approximately 350,000 hospitalizations, 5 million office visits, 276,000 emergency department

visits, and 234,000 outpatient visits to AF.[42] This translates to $26 billion in 2008 dollars.[43] In a retrospective, observational cohort study (administrative claims from the MarketScan Commercial and Medicare Supplemental research data bases from 2004 to 2006), 89,066 patients with AF that are 20 years or older with 1 or more inpatient or 2 or more outpatient AF diagnoses in 2005 were matched to non-AF control subjects. Over a 12-month period, 37.5% of patients with AF were hospitalized compared with 17.5% of control subjects, and 2.1% of patients with AF died during hospitalization compared with 0.1% of controlled subjects. The national incremental cost of AF was estimated to range from $6.0 to $26 billion. The total incremental cost of AF was $8705 per patient, with mean annual inpatient costs per patient 200% higher; outpatient medical costs were 63% higher, and outpatient pharmacy costs were 3% more than for control subjects (all P <.001).[43] A breakdown of distribution of direct costs for nonvalvular AF (NVAF) is shown in **Figure 3.**[42]

However, updated national statistics estimate substantial increases in healthcare utilization, with an estimated 750,000 hospitalizations per year due to AF[4] and private insurances report direct costs as high as $15,553 per year for enrollees with AF, compared with $3204 for enrollees without AF (2002 US$).[44] It is important to note that none of these costs include the substantial amount of dollars spent on treating conditions, like strokes caused by AF. Stroke-related costs are projected to triple, from $71.6 billion in 2012 to $184.1 billion by 2030.[45]

Finally, arrhythmias also have a substantial impact on the individual's productivity and quality of life. Employees with an arrhythmia are more likely to miss workdays, utilize more short-term disability, and have lower productivity output than employees without an arrhythmia.[46] By 2050, loss of earning is expected to be the highest cost contributor to the total cost of stroke.[47] Similar to VTE, AF presents a disease state for ACOs where the population is currently significantly undertreated or not treated optimally due to various factors; thus, the AF population presents a unique opportunity for ACOs to take a closer look at the standard of care issues in anticoagulation to improve quality and reduce outcomes and overall healthcare costs.

Disease Overview: Venous Thromboembolism

VTE is a multifactorial disorder in which the blood clots inappropriately, and it can often be fatal. It includes DVT, in which blood clots in the deep veins of the body, and PE, which occurs when a clot breaks off and results in blocking blood supply to the lungs.[7] In situ PE can also occur—after trauma to the chest, for example. However, it is not usually differentiated in clinical practice from a PE that arises due to a peripheral DVT because they are both diagnosed with a computed tomography angiogram (CTA). However, in situ PE does represent a distinct patient population with distinct treatment parameters.[48]

Symptoms of DVT include pain, tenderness, or swelling in the upper and, more commonly, in the lower extremities. A physical examination may indicate increased warmth, edema, erythema, and dilated veins on the chest wall or leg. The location of the development of thrombi in the extremities is related to the risk of PE.[10] Phlegmasia cerulean dolens, a limb-threatening manifestation of DVT, may occur in the presence of a malignancy or a prothrombotic condition. For PE, common symptoms include dyspnea, tachypnea, and pleuritic chest pain.[10]

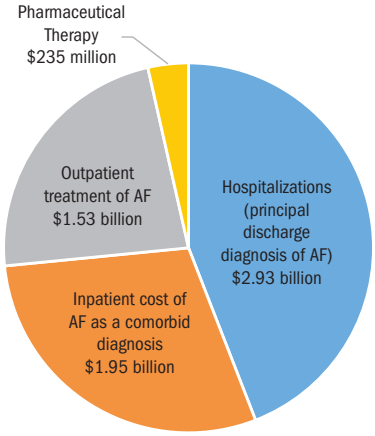
Although the exact etiology of VTE is not fully understood, it is known to be triggered through an interaction of multiple genetic and acquired risk factors, the latter consisting of transient and constant elements (see **Table 1**[7,8]).[7,8,49] Together these risk factors are known as thrombophilia or hypercoagulable states.[10]

Risk factors for VTE. Primary risk factors for VTE include increasing age, malignancy, major surgery, multiple trauma, prior VTE, chronic heart failure, and prolonged immobility.[50] However, not all risk factors are weighted equally. Strong risk factors for VTE include a hip or leg fracture, hip or knee replacement, major general surgery, major trauma, and spinal cord injury.[50] Additional risk factors associated with acute PE include cardiovascular risk factors, such as hypertension, diabetes mellitus, cigarette smoking, and high cholesterol levels.[10] When assessing patients for risk, it is important to understand the predictive value of these individual factors and weigh the cumulative risks accordingly.[50]

It is important to note that about half of all VTE cases are idiopathic, and 10% to 20% of cases have no acquired or genetic predisposition.[7,9,51,52] However, up to 5% of the US population does have a mutation for one of several genetic risk factors known as inherited thrombophilias (factor V Leiden [FVL], prothrombin G20210A mutation, protein C deficiency, protein S deficiency, and antithrombin deficiency).[8,51] For patients with heterozygous thrombophilias, the mutations may increase the risk of VTE by up to 10-fold.[7,8,53] The most common acquired thrombophilia, antiphospholipid antibody syndrome, is also among the more clinically important thrombophilias. It has a higher risk of developing into arterial and venous thrombosis as compared with others, and increases pregnancy-related complications.[54] Deficiencies of anticoagulants are related to a high risk of VTE, but the presence of one of these mutations, heterozygous or homozygous, does not always translate into the development of VTE.[7,8,53]

While it is possible to test patients for the genetic risk factors, diagnostic testing is problematic for a multitude of reasons. For example, factors shown to increase the risk of VTE in white people have little impact on the risk in black people with VTE. Furthermore, risk is based not just on the presence of these risk factors, but on a combination of genetic and environmental factors, as well as the extent of their presence. Those with more than 1 thrombophilia have a greater risk than individuals with a single mutation; women with FVL or sickle cell trait have a greater risk while they are on an oral contraceptive; and pregnancy also increases the risk in those with a genetic mutation.[7] Lastly, there are

Figure 3. Healthcare Utilization for Atrial Fibrillation (AF) (in 2005 US$)[42]



$6.65 billion in annual healthcare utilization for AF

likely many thrombophilias that are yet to be discovered.[49]

Diagnosis of VTE: DVT and PE. Diagnosis of DVT is often unreliable, so risk stratifications have been developed based on signs, symptoms, and risk factors.[10,55] The ACCP recommends a clinical assessment of pretest probability of DVT, rather than performing a routine set of diagnostic exams for the first lower extremity DVT. In patients with a low probability, initial testing with D-dimer or ultrasound of the proximal veins is recommended. Initial testing with a highly sensitive D-dimer, proximal compression ultrasound, or whole-leg ultrasound is recommended for patients with moderate risk, or pretest probability. A proximal compression or whole-leg ultrasound is recommended in patients with a high pretest probability. Unfortunately, due to lack of high-quality evidence, the ACCP does not have any recommendations for the assessment for recurrent DVT or upper extremity DVT.[55] Tests based on clinical prediction rules (Wells score or Geneva score) may also be used to assist in the diagnosis process.[10] If the Wells score shows that VTE is unlikely and the D-dimer test is negative, then further workup for VTE is typically not warranted.

The nonspecific symptoms that are characteristic of PR, such as shortness of breath, severe and sharp chest pain during breathing, coughing, and fast heart rate, make it difficult to diagnose. The American College of Physicians has developed "Rule-Out" criteria to determine the risk of PE in patients, and does not recommend testing for PE in patients with low risk. The criteria include the patient's medical history (ie, age, heart rate, oxygen saturation, leg swelling, hemoptysis, recent surgery or trauma, history of VTE, and estrogen use) and symptoms to determine the likelihood that PE has occurred. In patients suspected of PE, D-dimer testing, (which takes the patient's age into consideration) should be considered. Positive results should be followed by a CT scan. In patients with a high likelihood of PE, D-dimer testing is not required, and a CT scan should be ordered.[56]

A recent multi-level logistic regression analysis of data from the 2011 Nationwide Inpatient Sample of over 6.7 million hospitalizations of US adults demonstrated that among hospitalizations of adults, the presence of certain comorbidities and hospital contextual factors is significantly associated with the likelihood of VTE diagnosis. The study found that certain subgroups had higher rates of VTE diagnosis than others; specifically, these groups included adults aged over 80 years (3%), males (2.9%), black patients (2.7%), those with 7 or more days of hospital stay (5.7%), Medicare beneficiaries (2.9%), and those who did not require an operating room procedure (2.7%). Adults hospitalized with certain preexisting health conditions were almost 3 times more likely to be diagnosed with VTE than hospitalized adults without, and adults hospitalized in urban hospitals had a 15% increased likelihood of a VTE diagnosis than those treated in rural hospitals. The rate of VTE diagnosis was also influenced by bed size, ownership, and location of the hospital.[57] This study underscores the importance of evidence-based clinical practice that utilizes appropriate risk assessment and stratification to ensure effective management and prevention of VTE among hospitalized adults. Lastly, bleed risk factors and risk assessment should also be taken into consideration.

Disease Overview: Atrial Fibrillation

AF is a common rhythmic disturbance of the heart in which degeneration of the electrical impulses in the upper chambers of the heart (atria) results in the uncoordinated, chaotic activation of the atria characterized by tachycardic rhythm. The unpredictable conduction of these chaotic impulses move across the atrioventricular (AV) node into the lower cardiac chambers (ventricles), eventually resulting in the functional deterioration of the heart.[28,58] The disruption in electrical impulses may be caused by a variety of pathophysiological mechanisms, many of which are not fully understood (see **Figure 4**[40]). AF represents the common phenotypical end point of these mechanisms.[59]

Diagnosis and classification of AF. Electrocardiogram (ECG) characteristics of AF include irregular (R-R) intervals in the presence of AV conductance, absence of consistent P waves, and irregular atrial activity (rapid oscillations or fibrillatory waves that vary in size, shape, and timing).[28] As a diagnosis, AF is dynamic in nature, and the pattern of AF can change over time. The classification of AF can be based on the ECG pattern, epicardial or endocavitary recordings, mapping of atrial electrical activity, or clinical features.[59]

The American College of Cardiology (ACC), American Heart Association (AHA), and European Society of Cardiology, with the collaboration of the Heart Rhythm Society (HRS), have defined 4 sub-types for AF that can help classify AF in terms that are simple and clinically relevant. However, before applying subtypes, it is important to distinguish the first-detected episode of AF. An episode of AF is defined as an event lasting for 30 seconds or longer. After 2 episodes, the AF is considered recurrent.[59]

Table 1. Risk Factors Associated With Venous Thromboembolism[7,8]

GENETIC RISK FACTORS	ACQUIRED RISK FACTORS		MIXED/UNKNOWN
	CONSTANT	TRANSIENT	
• Family history • Inherited thrombophilias: • Factor V Leiden (FVL) • Prothrombin G20210A • Protein C deficiency • Protein S deficiency • Antithrombin deficiency • Sickle cell trait	• Advanced age • Antiphospholipid antibodies • Cancer • Chronic disease • Obesity • Myeloproliferative disorders • Polycythemia vera • Prior VTE	• Pregnancy • Oral contraceptives • Hormone replacement therapy • Hospitalization • Surgery • Major surgery • Orthopedic surgery • Trauma • Immobilization • Extended bed rest • Plaster cast • Central venous catheters	• High levels of: • Factor VIII • Factor IX • Factor XI • Fibrinogen • Thrombin activatable fibrinolysis inhibitor • Protein C inhibitor • Low levels of tissue factor pathway inhibitor • Activated protein C resistance in the absence of FVL • Hyperhomocysteinemia

The 4 sub-types are:

- Paroxysmal AF: recurrent AF that terminates spontaneously or with intervention (pharmacological therapy or direct-current cardioversion) within 7 days of onset.
- Persistent AF: arrhythmia that is continuous and sustained for more than 7 days.
- Long-standing persistent AF: uninterrupted arrhythmia of more than 12 months in duration.
- Permanent AF: cases of long-standing persistent AF, where cardioversion has failed or been foregone.

The categorizations of paroxysmal, persistent, long-standing, and permanent are not mutually exclusive. They exhibit overlapping features and are intended for the purpose of clarifying duration of episodes, length of diagnosis, and treatment intention. Finally, NVAF is defined as AF that occurs without rheumatic mitral stenosis, a prosthetic heart valve, or mitral valve repair,[59] with approximately 95% of atrial fibrillation being nonvalvular and the remaining 5% being valvular.[60]

Risk factors for AF. A parental history of AF is associated with increased odds of AF—a 1.85-fold increase in risk in the adult if 1 parent has AF (multivariable-adjusted 95% CI, 1.12-3.06; $P = .02$). Specific single-nucleotide polymorphisms have also been associated with AF in patients with specific ancestries.[29] Additionally, a variety of cardiovascular conditions have been associated with increasing the risk of AF by causing arterial dilation, thereby promoting electrical instability. AF is also a common postoperative complication in cases of myocardial infarction and in patients who have recently undergone cardiac or thoracic surgery.[28] Arrhythmia resulting from conditions associated with the risk of AF may be alleviated by the treatment of the underlying condition.28,35 For a thorough list of factors that may contribute to AF, see Table 2.[28,35,59,61]

Diagnosis of AF. The clinical manifestations of AF are variable, and some patients may even be asymptomatic. Most patients tend to experience a combination of symptoms, which may include an irregular heartbeat, heart palpitations (rapid, fluttering, or pounding), lightheadedness, fatigue, dyspnea, polyuria (due to release of atrial natriuretic peptide), or chest pain. The extent of the symptoms can vary based on the ventricular rate, the patient's underlying health or functional status, and duration of AF. Because the degree of severity of some of these symptoms is subjective, the individual patient's perceptions may also be of consequence. Although uncommon, syncope is a serious complication associated with AF, as well.[4,28]

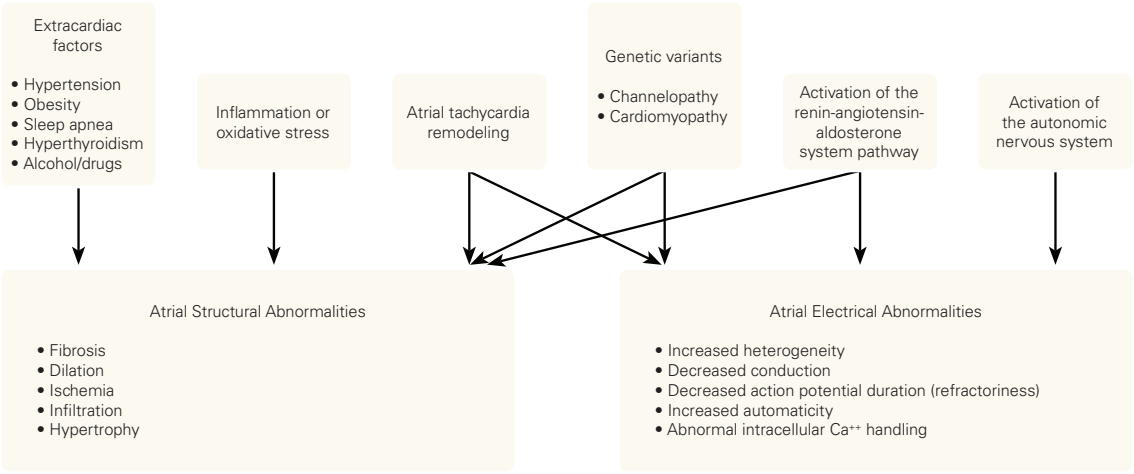
The diagnosis of AF in a patient is based on the patient's clinical history and physical examination and is confirmed by ECG, sometimes in the form of ambulatory rhythm monitoring (ie, telemetry, Holter monitor, event recorders) or implanted devices. The initial evaluation involves characterizing the pattern of the arrhythmia, reviewing the patient's family and medical history, noting symptoms, and defining the associated etiology for associated conditions and potentially reversible risk factors.[40] A thorough and appropriate diagnosis is critical in ensuring an effective management strategy.

Treatment of VTE and AF: Guidelines for Their Management

Management of VTE. The AT9 guidelines by the ACCP focus on the risk stratification of patients and suggest that clinicians should consider a patient's risk for VTE and bleeding before administering or prescribing a prophylactic drug or device. This trend is reflected in the recommendations from the ACCP for the prevention as well as the management of thrombosis.[27,55]

The goal of treatment for DVT is the prevention of PE , extension of the clot, and recurrent VTE.[10] Initial therapy with an anticoagulant such as UFH, LMWH, or fondaparinux, followed by a vitamin K antagonist (VKA) such as warfarin, initiated on day 1 or 2 of LMWH/UFH therapy, has traditionally been the first step towards achieving this goal.[10] Routine use of pharmacogenetic testing for warfarin dosing is not recommended in these

Figure 4. Mechanisms of Atrial Fibrillation[40]



Adapted from January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol.* 2014;130(23):2071-2104.

patients.[61] All 4 DOACs—dabigatran, rivaroxaban, apixaban, and edoxaban—are also now approved for use in the United States for VTE treatment, with the caveat that edoxaban does not carry an indication for extended treatment after an initial course of therapy, while the other 3 DOACs do have this indication.

Management of AF. Management of AF is focused on stroke prevention with antithrombotic and antiplatelet therapies. Joint guidelines by the AHA/ACC/HRS recommend that treatment be individualized based on risk stratification for stroke and bleeding. It is recommended that selection of antithrombotic therapy be based on the risk of thromboembolism, irrespective of the pattern of AF (ie, paroxysmal, persistent, or permanent), and it is important to utilize shared decision making with the patient when deciding on the best approach.[40]

Warfarin remains the drug of choice for patients with valvular AF or mechanical or bioprosthetic heart valves, as DOACs are not currently approved for these indications. INR testing is recommended on a weekly basis, at least, during initiation of treatment with warfarin, and at least monthly when INR is in range and anticoagulation is considered stable. All patients should be reevaluated periodically for the risk of bleeding and stroke, and to determine if antithrombotic therapy is still warranted, and if so, if the current antithrombotic choice is still the best option.[40,59] When treatment with warfarin needs to be interrupted peri-procedurally, bridging with LMWH should not be utilized, based on the results of the recently published BRIDGE trial that showed no reduction in thromboembolic events and a significantly increased rate of major bleeding in the patients who were bridged.[62]

Traditional Treatment Options for VTE and AF

Regarding VKA adherence in a study of 4188 patients, UFH, LMWH, fondaparinux, and warfarin have long been the basic building blocks of antithrombotic therapy, with warfarin being available since the mid-1950's. ACCP guidelines recommend LMWH over UFH for the initial treatment of DVT or PE. LMWH is renally cleared and may be used in patients with renal insufficiency, and although monitoring is recommended, it is not required. However, in general, UFH should be preferred in patients with CrCl <20 mL/min.[27] Fondaparinux, an indirect factor Xa inhibitor, is approved as treatment for acute DVT and PE when used in combination with a VKA, but is contraindicated in patients with CrCl <30 mL/min. In general, anticoagulants demonstrate strong reductions in recurrent VTE and stroke in patients with VTE and AF.[63,64]

Warfarin has been the mainstay of long-term treatment of VTE.[10] It is water-soluble and rapidly absorbable, and has high bioavailability. Warfarin interferes with the formation of vitamin K-dependent clotting factors, resulting in the hepatic production of partially carboxylated and decarboxylated proteins that have reduced coagulant activity.[65] However, treatment with warfarin requires routine laboratory monitoring, has variable patient response, and is associated with multiple drug-drug and drug-food interactions.[59,65,66] In addition, warfarin has a narrow therapeutic index, delayed onset (3-7 days) and offset of action, high bleeding rates, and slow reversibility with phytonadione (vitamin K), with peak effects occurring about 18 to 20 hours after the administration. Genetic and environmental factors can influence warfarin's absorption, pharmacokinetics, and pharmacodynamics, thereby influencing its dose on an individual level.[65] Advancing age also impacts the dose of warfarin. The availability of vitamin K stores decrease with age, thus reducing the dose requirement for warfarin.[67,68] Concomitant use of certain antibiotics and nonsteroidal

Table 2. Factors Contributing to the Risk of Atrial Fibrillation[28,35,59,61]

PREDICTORS OF 10-YEAR RISK	RISK FACTORS, CAUSES, AND ASSOCIATED CONDITIONS	DIAGNOSTICS	BIOMARKERS
• Age • Male sex • Body mass index • Systolic blood pressure • Treatment for HTN • PR interval • Significant murmur • Prevalent heart failure	• Cardiovascular diseases • HTN, especially with LVH • CAD disease • Systolic HF • Valvular heart disease (often mitral) • Pulmonary diseases • COPD • PE • Hyperthyroidism • Diabetes mellitus • Alcohol intake • Surgery • Electrolyte abnormalities • Electrocution • European ancestry • Family history • Genetic variants	• Electrocardiogram • LVH • Echocardiograph • LA enlargement • Decreased LV fractional shortening • Increased LV wall thickness	• Increased CRP • Increased BNP

BNP indicates B-type natriuretic peptide; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; HF, heart failure; HTN, hypertension; LA, left atrial; LV, left ventricular; LVH, left ventricular hypertrophy; MI, myocardial infarction; PE, pulmonary embolism; PR interval (interval in milliseconds from the P wave to the R wave on the ECG); VHD, valvular heart disease.

anti-inflammatory drugs (NSAIDs), including COX-2 inhibitors, is not recommended in patients taking VKAs. Concomitant treatment with antiplatelet agents should also be as minimized as much as possible. For patients who no longer need treatment with a VKA, gradual tapering of the dose is not needed.[66] These factors contribute to a complex dosing regimen that requires vigilant and resource-intensive management to ensure optimal dosing and balance between the risk of bleeding and thrombosis.

A human prothrombin complex concentrate, k-centra, is a recently approved, intravenous blood coagulation factor replacement product indicated for the urgent reversal of acquired coagulation factor deficiency induced by warfarin or other VKAs in adult patients with acute major bleeding or the need for urgent surgery or other invasive procedure.[69] It contains factors II, VII, IX, X, proteins C and S, and minimal amounts of heparin.

In a study of 4188 patients who were newly starting warfarin therapy to prevent AF-related thromboembolism, more than 25% of patients discontinued treatment, defined as 180 consecutive days or more off warfarin, within 1 year of initiation. Patients less than 65 years old were more likely to discontinue treatment than those 85 years or older (HR, 1.33; 95% CI, 1.03-1.72).[58] Approximately 50% of patients who have NVAF are on an antithrombotic, which may be partially due to the difficulty in monitoring patients on warfarin, especially in rural areas.[70-73] A meta-analysis of 8 studies found that warfarin patients with AF only spend about 55% of time in the therapeutic range. These adherence and dosing challenges are problematic for the long-term effectiveness of the drug, and the lack of adherence results in an unfortunate gap between effectiveness seen in clinical trials and those seen in the real-world setting: use of warfarin in clinical practice results in only a 35% reduction in ischemic strokes, compared with a 64% reduction demonstrated in controlled clinical trials.[74] Discontinuation of treatment among high-risk patients with VTE increases the risk of recurrent VTE events,[75] and the number of days on treatment is inversely proportional to the likelihood of hospitalization (P <.001) and emergency department visits (P = .019). Patients who receive warfarin also incur lower total costs (P <.001) than patients who do not receive warfarin.[76]

To ensure adherence and improve efficacy, the ACCP recommends that oral anticoagulation VKA therapy only be prescribed in a systematic and coordinated manner, one in which patients are well-educated about their disease and the need for treatment, systematic INR testing, tracking for adherence, follow-up, and good patient communication of results and dose decisions.[27] Although traditional therapeutic options are effective and safe, their administration is cumbersome for patients and physicians because LMWH often needs to be administered via daily or twice-daily subcutaneous injections, and warfarin requires frequent coagulation monitoring and dose adjustments to ensure that the INR remains therapeutic. DOACs offer patients an alternative to warfarin, and they are more convenient and, in many cases, more effective and safe depending on the agent and the indication, without the need for routine INR monitoring such as with warfarin.

New Direct Oral Anticoagulants

The inherent drawbacks of warfarin have prompted development and increasing utilization of DOACs, which offer more selective inhibition of factor Xa and thrombin, key factors within the coagulation cascade.[77,78] DOACs offer a safe and effective alternative to warfarin.[78,79] They have fixed dosing regimens without routine monitoring, are rapidly absorbed, have a wide therapeutic window, onsets within 30 minutes, and produce peak plasma concentrations within 1 to 4 hours.[80] DOACs also have fewer drug-drug and dietary interactions, as well as low inter- or intra-individual

Table 3. Comparison of Direct Oral Anticoagulants for Venous Thromboembolism and Nonvalvular Atrial Fibrillation[85,88,89,91-93]

	Dabigatran (Pradaxa)	Rivaroxaban (Xarelto)	Apixaban (Eliquis)	Edoxaban (Savaysa)
MOA	Direct thrombin inhibitor	Direct FXa inhibitor	Direct FXa inhibitor	Direct FXa inhibitor
Indication for VTE	• Treatment of DVT and PE, and for the reduction in the risk of recurrence of DVT and of PE in patients who have been treated with a parenteral anticoagulant for 5-10 days	• Treatment of DVT and PE, and for the reduction in the risk of recurrence of DVT and of PE	• Treatment of DVT and PE, and for the reduction in the risk of recurrence of DVT and of PE	• Treatment of DVT and PE after 5 to 10 days of initial therapy with a parenteral anticoagulant
Dosing for an Initial VTE Course	• 150 mg BID orally after 5-10 days of parenteral anticoagulation • CrCl <30 mL/min: not indicated	• 15 mg BID orally with food for 3 weeks; then 20 mg QD with food • May be used as monotherapy • CrCl <30 mL/min: not indicated	• 10 mg BID orally for 7 days; then 5 mg BID • May be used as monotherapy • No dosage adjustment necessary for renal impairment	• 60 mg QD orally • CrCL 15-50 mL/min or body weight ≤60 kg: 30 mg QD • After 5-10 days parenteral treatment (LMWH) needed • CrCl <30 mL/min: not indicated
Dosing for Extended VTE treatment	• 150 mg BID • CrCl <30 mL/min: not indicated	• 20 mg QD with food • CrCl <30 mL/min: not indicated	• 2.5 mg BID • No adjustment necessary for renal impairment	• No indication
Indication for NVAF	• Reduce risk of stroke and SE in patients with NVAF	• Reduce risk of stroke and SE in patients with NVAF	• Reduce risk of stroke and SE in patients with NVAF	• Reduce risk of stroke and SE in patients with NVAF • Should not be used in patients with CrCL >95 mL/min due to increased risk of ischemic stroke compared with warfarin at the highest dose studied (60 mg)
Dosing for NVAF	• CrCl >30 mL/min: 150 mg BID • CrCl 15-30 mL/min: 75 mg BID • CrCl <15 mL/min: not indicated	• CrCl >50 mL/min: 20 mg QD with evening meal • CrCl 15-50 mL/min: 15 mg QD with evening meal • CrCl <15 mL/min: not indicated	• 5 mg BID • 2.5 mg BID in patients with at least 2 of the following: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL • CrCl <15 mL/min or ESRD on HD: 5 mg BID or 2.5 mg BID if ≥80 years or ≤60 kg.	• CrCl >50 to ≤95 mL/min: 60 mg QD • CrCl >15 to ≤50 mL/min: 30 mg QD • CrCl <15 mL/min: not indicated

BID indicates twice a day; CrCl, creatinine clearance; ESRD, end-stage renal disease; FXa, Factor Xa; HD, hemodialysis; LMWH, low-molecular weight heparin; MOA, mechanism of action; NVAF, nonvalvular atrial fibrillation; PE, pulmonary embolism; QD, once daily SE, systemic embolism; VTE, venous thromboembolism.

variability, producing a predictable anticoagulant response that renders routine INR monitoring and dose adjustments unnecessary. Because of their rapid onset and offset of action, the DOACs have the potential to replace parenteral anticoagulants and warfarin for initial, long-term, and extended VTE and NVAF treatment.[77-82]

However, these agents are not without limitations. Use of DOACs is contraindicated in those with mechanical prosthetic heart valves and valvular AF. DOACs are all renally excreted to varying degrees (27%-85%) and have different recommendations for use in renal insufficiency depending on the indication (see Table 3[85,88,89,91-93]). Additional limitations include a lack of standardized monitoring in urgent scenarios, inconsistent availability of an approved antidote for factor Xa inhibitors (andexanet alfa is under investigation in phase 4 trials; it binds and inhibits direct and indirect factor Xa inhibitors), and higher drug acquisition cost.[77,78,82,86] Similar to warfarin, concomitant use of NSAIDs and antiplatelets will increase bleed risk. Recent real-world analyses are now reinforcing the DOACs' safety profiles, and overall costs (versus drug acquisition costs) appear to be lower with DOACs versus warfarin (see section on *Cost-Effectiveness of New Direct Oral Anticoagulants*).

All 4 DOACs currently on the market (dabigatran, rivaroxaban, apixaban, and edoxaban) are FDA-approved for treatment of VTE and NVAF. While none of the DOACs require routine INR monitoring, baseline hepatic function, baseline and ongoing renal function, as well as drug-drug interactions, should be intermittently assessed every 3, 6, or 12 months, depending on the patient's clinical presentation.

DOAC use versus warfarin use in patients with NVAF was recently assessed in a meta-analysis of the phase 3 trials, including the RE-LY, ROCKET AF, ARISTOTLE, and ENGAGE AF-TIMI 48 trials.[85] From the participants analyzed in the meta-analysis, 42,411 received a new oral anticoagulant and 29,272 received warfarin. Compared with warfarin, DOACs significantly reduced stroke or systemic embolic events by 19% (relative risk [RR], 0.81; 95% CI, 0.73-0.91; P <.0001), all-cause mortality by 10% (RR, 0.90; 95% CI, 0.85-0.95; P = .0003), and intracranial hemorrhage by 52% (RR, 0.48, 95% CI, 0.39-0.59; P <.0001). Low-dose DOACs demonstrated similar results for stroke or systemic embolic events compared with warfarin (RR, 1.03, 95% CI, 0.84-1.27; P = .74), as well as a 35% more favorable bleeding profile (RR, 0.65, 95% CI, 0.43-1.00; P = .05). However, use of DOACs did result in a 25% increased risk of gastrointestinal bleeding (RR, 1.25, 95% CI, 1.01-1.55; P = .04) compared with warfarin, and patients taking low-dose DOACs had significantly more ischemic strokes (RR, 1.28, 95% CI, 1.02-1.60; P = .045) compared with patients at 28% taking warfarin.[87]

Rivaroxaban. Rivaroxaban is a factor Xa inhibitor approved for stroke prevention in NVAF, VTE prevention in hip and knee replacement surgery, VTE treatment, and extended VTE treatment.[88] It is typically a once-daily drug, except for during VTE initiation, when it is taken twice daily. For VTE treatment, initial treatment is 15 mg twice daily for 21 days, and then decreases to 20 mg daily on day 22. Dosing for reduction in recurrent VTE after an initial course is also 20 mg daily. Rivaroxaban 15 and 20 mg doses should be taken with large meals for increased absorption. Rivaroxaban has a rapid onset of action, reaching its peak effect in 2 to 3 hours with a half-life of 5 to 9 hours in individuals aged 20 to 45 years. The half-life is extended to 11 to 13 hours in elderly patients.[86] Rivaroxaban is a partially renally excreted drug (~36% unchanged drug), and clearance is decreased with increasing renal impairment. However, it has a moderate influence on renal function, even in patients with severe renal impairment.[79,87] Concomitant use of rivaroxaban should be avoided with drugs that are potent dual inhibitors or inducers of CYP3A4 and permeability-glycoprotein (P-gp).[88,89]

A randomized double-blind trial (ROCKET AF) of 14,264 patients comparing fixed-dose rivaroxaban (20 mg daily) with adjusted dose warfarin found that rivaroxaban was noninferior to warfarin in reducing risk of stroke and non–central nervous system embolism (SSE) in patients with NVAF (HR, 0.88; 95% CI, 0.74-1.03; P <.001 for noninferiority). In addition, a pre-specified analysis demonstrated superiority in SSE reduction in the on-treatment arm.[83] Rivaroxaban was also associated with lower risk of intracranial bleeding (0.5% vs 0.7%; P = .02) and fatal bleeding (0.2% vs 0.5%; P = .003). However, gastrointestinal bleeding occurred more often in the rivaroxaban group (3.2% vs 2.2%, respectively; P <.001).[83] In the pooled analysis of the EINSTEIN DVT and PE trials, 8282 patients with proximal DVT or PE received either rivaroxaban as monotherapy or enoxaparin plus an oral VKA such as warfarin.[90] Symptomatic recurrent VTE rates were similar between the 2 groups: 2.1% for the rivaroxaban group compared with 2.3% in the standard therapy group. Major bleeding was significantly less in the rivaroxaban group (1%) compared with the standard therapy group (1.7%) (HR, 0.54; 95% CI, 0.37-0.79; P = .002), demonstrating a 0.7% absolute reduction in major bleeding with rivaroxaban. In the extended VTE treatment study for an additional 6 or 12 months in patients who had completed an initial 6 to 12 months of treatment for VTE, rivaroxaban had superior efficacy to placebo with similar major bleeding but an increase in overall bleeding. Net clinical benefit clearly favored rivaroxaban over placebo.[84,91]

Efficacy and safety of rivaroxaban (subcutaneous placebo for 10 ± 4 days and oral rivaroxaban, 10 mg once daily, for 35 ± 4 days) was further assessed for an extended period in hospitalized patients with acute medical illnesses, compared with subcutaneous enoxaparin administered for a standard period (40 mg once daily, for 10 ± 4 days), followed by placebo (35 ± 4 days). Rivaroxaban was noninferior to enoxaparin at day 10 (with rivaroxaban: RR, 0.97; 95% CI, 0.71-1.31; P = .003 for noninferiority) and superior at day 35 (RR, 0.77; 95% CI, 0.62-0.96; P = .02). Overall, extended-duration rivaroxaban reduced the risk of VTE, although it was associated with an increased risk of bleeding and thus does not carry a current indication for this population.[92]

Rivaroxaban 10 mg PO once daily was compared with enoxaparin in the 4 RECORD trials.[95-97] RECORD1 and RECORD2 evaluated patients after total hip replacement and RECORD3 and RECORD4 assessed patients following total knee replacement. All 4 RECORD trials showed that rivaroxaban was superior to enoxaparin in preventing VTE. Additionally, the RECORD4 study of total knee arthroplasty showed that rivaroxaban demonstrated superiority over enoxaparin 30 mg SQ every 12 hours for VTE prophylaxis.[98]

Apixaban. A twice-daily drug, apixaban is also an oral factor Xa inhibitor approved for stroke prevention in NVAF, VTE prevention in hip and knee replacement surgery, VTE treatment, and extended VTE treatment. It has a rapid onset of action, reaching its peak effect in 3 to 4 hours and a half-life of 12 hours. It has a renal clearance of 25%. Apixaban is the only DOAC approved for use in patients on dialysis. Concomitant use of apixaban should be avoided, or at least dose reduced when possible, with drugs that are potent dual inhibitors or inducers of CYP3A4 and P-gp.[85]

The ARISTOTLE trial of 18,201 patients demonstrated superior efficacy of apixaban to warfarin in reducing the risk of

stroke and systemic embolism in patients with AF (HR, 0.79; 98% CI, 0.66-0.95; $P = .01$). There was also significantly less major bleeding (2.13 % per year compared with 3.09 % per year; HR, 0.69; 95 % CI, 0.60-0.80; $P < .001$) and significantly lower mortality (3.52% vs 3.94%; HR, 0.89; 95% CI, 0.80-0.99; $P = .047$) in the apixaban group compared with the warfarin group. Treatment with apixaban was also associated with a lower rate of intracranial hemorrhage in comparison with warfarin.[99] AVERROES, a randomized, double-blind study, examined the use of apixaban (5 mg twice daily) compared with aspirin (81-324 mg daily) in patients (N = 5599) with AF who were at increased risk for stroke, and for whom VKA therapy was unsuitable.[98] Common reasons for warfarin unsuitability were: patient unable to obtain INRs at requested intervals; patient refused VKA therapy; clinical equipoise due to CHADS score of 1; INR unable to be maintained in therapeutic range; and patient not expected to be adherent to warfarin therapy. The trial was stopped early because a pre-specified interim analysis demonstrated that apixaban was superior to aspirin, and after a 1.1-year follow-up, was associated with a 55% reduction in the risk for stroke ($P < .001$). The risk of major bleeding was not significantly increased with apixaban compared with aspirin (1.4% vs 1.2% per year; HR, 1.13; 95% CI, 0.74-1.75; $P = .57$), although as expected, overall bleeding was increased.[100]

The AMPLIFY study of 5395 patients compared apixaban as monotherapy with conventional therapy (subcutaneous enoxaparin followed by warfarin) for the treatment of acute VTE. Apixaban was noninferior to conventional therapy with 2.3% of patients in the apixaban group and 2.7% in the conventional therapy group having recurrent VTE (RR, 0.84; 95% CI, 0.60-1.18). Apixaban was associated with significantly less major bleeding (0.6% vs 1.8% in the conventional group; RR, 0.31; 95% CI, 0.17-0.55; $P < .001$).[93] AMPLIFY-EXT compared apixaban with placebo in patients who had completed an initial course of at least 6 months of standard anticoagulant therapy for VTE. Recurrent VTE or death was significantly reduced at 12 months in patients taking apixaban ($P < .001$) without increasing the rate of major bleeding.[101]

Use of apixaban as prophylaxis for VTE for an extended period in medically ill patients beyond hospital discharge was studied in a double-blind, double-dummy, placebo-controlled trial. The ADOPT trial included 6528 acutely ill patients who were hospitalized for at least 3 days with congestive heart failure, respiratory failure, or another medical disorder, and had at least 1 additional risk factor for VTE. They were randomized to receive oral apixaban (2.5 mg BID for 30 days), or subcutaneous enoxaparin (40 mg once daily for 6 to 14 days). The extended course of apixaban was not superior to the short course of enoxaparin for the primary outcome: 30-day composite of death related to VTE, PE, or symptomatic or asymptomatic DVT (with apixaban: RR, 0.87; 95% CI, 0.62-1.23; $P = .44$). Apixaban was also associated with significantly more major bleeding events than was enoxaparin (RR, 2.58; 95% CI, 1.02-7.24; $P = .04$) and thus does not carry a current indication in this population.[102]

Apixaban is also approved for the prevention of DVT after elective knee or hip surgery. Apixaban 2.5 mg twice daily initiated 12 to 24 hours postoperatively was evaluated in three phase 3 studies of patients having hip or knee arthroplasty.[99-105] Two studies compared this regimen with enoxaparin 40 mg once daily (EU dosing; the ADVANCE-2 and ADVANCE-3 studies) and the third compared it with enoxaparin 30 mg twice daily (US dosing; ADVANCE-1).[103-105] Overall, apixaban was more effective in preventing DVT compared with enoxaparin, without a significant increase in bleeding risk.

Edoxaban. Edoxaban was the third oral factor Xa inhibitor to be approved for stroke prevention in NVAF and an initial course of VTE treatment and is also a once-daily drug. It has a rapid onset of action of around 30 minutes, reaching its peak effect in 1 to 2 hours; it has a half-life of 10 to 14 hours.[92] It has a renal clearance of approximately 35% to 39%, while the remainder is excreted via the feces. Concomitant use of edoxaban and rifampin, a strong P-gp inducer, should be avoided.[80,92]

In the ENGAGE-AF TIMI-48, a 3-group trial of 21,105 patients, edoxaban demonstrated noninferiority to warfarin in the risk reduction of stroke in patients with AF. The high-dose edoxaban group received 60 mg once daily while the low-dose group received 30 mg once daily and these doses were halved for estimated CrCl of 30 to 50 mL/min, body weight of 60 kg or less, or concomitant use of potent P-gp inhibitors.

The annualized rate of the primary end point during treatment was 1.50% with warfarin as compared with 1.18% with high-dose edoxaban (HR, 0.79; 97.5% CI, 0.63-0.99; $P < .001$ for

To learn more about VTE and AF, or to find resources to recommend to your patients, please visit:

Centers for Disease Control and Prevention
- www.cdc.gov/ncbddd/dvt/index.html
- www.cdc.gov/dhdsp/data_statistics/fact_sheets/fs_atrial_fibrillation.htm

The National Heart, Lung, and Blood Institute
- www.nhlbi.nih.gov/health/health-topics/topics/dvt
- www.nhlbi.nih.gov/health/health-topics/topics/af

World Thrombosis Day
- www.worldthrombosisday.org

ClotCare Online Resource: Provide patients and healthcare providers with up-to-date information and expert insight on optimal use of antithrombotic and anticoagulant therapy.
- www.clotcare.com/

Anticoagulation Forum: Provider of education and an authoritative voice among anticoagulation professionals.
- www.acforum.org/

International Society on Thrombosis and Haemostasis (ISTH): A global not-for-profit organization advancing the understanding, prevention, diagnosis, and treatment of thrombotic and bleeding disorders.
- www.isth.org/

noninferiority), and 1.61% with low-dose edoxaban (HR, 1.07; 97.5% CI, 0.87-1.31; *P* = .005 for noninferiority). The annualized rate of major bleeding was 3.43% with warfarin versus 2.75% with high-dose edoxaban (HR, 0.80; 95% CI, 0.71-0.91; *P* <.001) and 1.61% with low-dose edoxaban (HR, 0.47; 95% CI, 0.41-0.55; *P* <.001).[106] The FDA approved dose for NVAF is edoxaban 60 mg daily for patients with CrCl >50 and ≤95 mL/min and is not recommended for use with CrCL >95 mL/min. Dosage should be reduced to 30 mg daily in patients with CrCl of 15 to 50 mL/min.

In the Hokusai VTE study of 4921 patients with DVT and 3319 patients with PE, edoxaban, after at least 5 days of parenteral therapy lead-in, demonstrated noninferiority to standard therapy including warfarin for recurrent VTE (HR, 0.89; 95% CI, 0.70-1.13; *P* <.001). For the primary safety endpoint, edoxaban demonstrated significantly lower rates of major or clinically relevant nonmajor bleeding (HR, 0.81; 95% CI, 0.71-0.94; *P* = .004 for superiority). While there was no difference in major bleeding between the 2 groups, there were numerically fewer fatal bleeds and fatal intracranial bleeds with edoxaban (2 vs 10 and 0 vs 6, respectively).[109] For VTE treatment, the FDA approved dose of edoxaban is 60 mg daily and this is reduced to 30 mg daily for patients with CrCL between 15 to 50 mL/min or body weight less than or equal to 60 kg or who use certain P-gp inhibitors.

Dabigatran. Dabigatran is a direct thrombin inhibitor approved for prevention of stroke in NVAF, VTE treatment, and extended VTE treatment after an initial course. It has a rapid onset of action of less than 30 minutes, reaching its peak effect in 1 to 2 hours, and has a half-life of 12 to 17 hours. It has a renal clearance of 80%. In NVAF, for concomitant use of dabigatran, potent P-gp inhibitors, and CrCl >30 mL/min, the dose should be reduced to 75 mg po BID, and if CrCl is 15 to 30 mL/min, concomitant use of dabigatran and P-gp inhibitors should be avoided. For VTE treatment in patients with CrCl <50 mL/min, concomitant administration of dabigatran and potent P-gp inhibitors or inducers should be avoided. Lastly, coadministration of P-gp inducers (ie, rifampin) and dabigatran should also be avoided.[93]

The RE-LY trial randomized 18,113 patients in an open-label, noninferiority trial, comparing 2 doses (in a blinded fashion) of dabigatran, 110 mg and 150 mg, with adjusted-dose warfarin. The lower dose of dabigatran was noninferior to warfarin in reducing the risk of stroke or systemic embolism (1.53% vs 1.69%, respectively; with dabigatran: RR, 0.91; 95% CI, 0.74-1.11; *P* <.001 for noninferiority). However, at the dose of 150 mg, dabigatran provided superior risk reduction compared with warfarin (1.11% vs 1.69%; RR, 0.66; 95% CI, 0.53-0.82; *P* <.001 for superiority). The rate of hemorrhagic stroke was 0.38% per year in the warfarin group, as compared with 0.12% per year with 110 mg of dabigatran (*P* <.001) and 0.10% per year with 150 mg of dabigatran (*P* <.001). The rate of major bleeding was 3.36% per year in the warfarin group, whereas it was 2.71% per year in the group receiving 110 mg of dabigatran (*P* = .003) and 3.11% per year in the group receiving 150 mg of dabigatran (*P* = .31). Only the 150 mg twice-daily dosing is approved in the United States. Rates of intracranial bleeding were significantly lower in both dabigatran groups, but there was a significantly higher rate of major gastrointestinal bleeding with dabigatran at the 150 mg dose than with warfarin.[108] Interestingly for the NVAF trials, dabigatran 150 mg BID was the only DOAC to demonstrate a significantly lower rate of ischemic stroke versus warfarin. Most of the other reductions in the incidence of strokes from DOACs were primarily reductions in hemorrhagic strokes.

After 5 to 10 days of parenteral anticoagulation lead-in, dabigatran was evaluated against warfarin in acute VTE in the RE-COVER and RE-COVER II trials; a pooled analysis of these studies was done to demonstrate hazard ratios for recurrent VTE of 1.09 (95% CI, 0.76-1.57), for major bleeding of 0.73 (95% CI, 0.48-1.11), and for any bleeding of 0.70 (95% CI, 0.61-0.79). Dabigatran demonstrated it was noninferior to dose-adjusted warfarin in the prevention of recurrent VTE with similar risk of major bleeding, but significantly less overall bleeding, between the 2 therapies.[109] In the RE-MEDY and RE-SONATE trials, dabigatran was compared with warfarin or placebo after at least 3 months of anticoagulation therapy. Dabigatran was effective in the extended treatment of VTE and carried a lower risk of major or clinically relevant bleeding than warfarin but a higher risk than placebo, although net clinical benefit favored dabigatran over placebo.[110]

The FDA has recently approved idarucizumab (Praxbind) for reversal of the anticoagulant effects of dabigatran in patients with life-threatening or uncontrollable bleeding or when reversal is needed for an emergent or urgent surgery or procedure.[111] When given as a 5 g bolus, idarucizumab demonstrates immediate and sustained reversal of dabigatran, and the availability of this agent will likely significantly improve patient care and safety as related to dabigatran use.

Cost-Effectiveness of New Direct Oral Anticoagulants

One of the main concerns with the use of DOACs has been the higher drug acquisition cost. However, real-world and hypothetical statistical analysis have demonstrated the overall cost-effectiveness of these agents in comparison with warfarin when safety and quality-adjusted life-years (QALYs) are taken into account, despite higher acquisition cost.

Over a 10-year time horizon, rivaroxaban demonstrated cost-effectiveness with potential cost savings compared with warfarin as a prophylactic anticoagulant for the prevention of recurrent VTE. The hypothetical cohort was composed of patients aged 60 years with an initial VTE who received secondary prophylaxis with either rivaroxaban or warfarin for 3 to 12 months. Treatment with rivaroxaban in this hypothetical analysis cost substantially less than warfarin ($3195 vs $6188, respectively) and was more effective (9.29 vs 9.14 QALYs).[112]

Real-world estimates of medical cost avoidances from a US payer perspective indicated that annual medical costs are reduced when DOACs are used instead of warfarin for treatment of patients with acute VTE. Treatment with apixaban resulted in an estimated avoidance of $4440 in annual total medical costs per patient-year compared with warfarin. Similarly, annual total medical cost avoidances versus warfarin were $2971 per patient-year for rivaroxaban, $1957 per patient-year for edoxaban, and $572 per patient-year for dabigatran.[113]

In a hypothetical health plan population of 1 million members, treatment with DOACs resulted in a savings of $204, $140, $495, and $340 per patient for dabigatran, rivaroxaban, apixaban, and edoxaban, respectively, compared with warfarin. This translated to medical-cost differences of –$3.7 million, –$4.2 million, –$11.5 million, and –$6.6 million for NVAF and acute patients with VTE treated with dabigatran, rivaroxaban, apixaban, and edoxaban, respectively. The cost savings were even higher when the extended VTE patient population was included, and the overall cost differences with DOACs were projected to increase over time.[114]

When extrapolated over a lifetime, 1 economic model found that dabigatran was cost-effective compared with warfarin in patients with AF, regardless of age of treatment initiation. Based on costs obtained from Medicare payment schedules and utilities from publications, the clinical event costs avoided per patient with the use of dabigatran were $1100, $135, and $713 for cohorts aged under 75 years, 75 years or older, and the overall population, respectively. Furthermore, extrapolating over a lifetime, dabigatran resulted in lower rates of stroke and intracranial hemorrhage for all age cohorts compared with warfarin, but higher rates for extracranial hemorrhage. Use of dabigatran resulted in incremental cost-effectiveness ratios of $52,773, $65,946, and $56,131 for cohorts aged under 75 years, 75 years or older, and all, respectively.[115]

Another study estimating the cost-effectiveness of stroke prevention in a hypothetical cohort of 70-year-old patients with NVAF, increased risk for stroke (CHADS2 ≥1), and CrCl ≥50 mL/min found that warfarin had the lowest cost ($77,813), followed by rivaroxaban ($78,738), dabigatran ($82,719), and apixaban ($85,326). However, apixaban had the highest QALY estimate (8.47), followed by dabigatran (8.41), rivaroxaban (8.26), and warfarin (7.97). Overall, the probabalistic sensitivity analysis showed that apixaban, dabigatran, rivaroxaban, and warfarin were cost-effective in 45.1%, 40%, 14.9%, and 0% of the simulations, respectively, with cost-effectiveness dependent on therapy pricing and on neurological events associated with rivaroxaban.[116]

To summarize, it appears that despite higher drug acquisition costs, DOACs have lower overall costs and are cost-effective or cost-neutral compared with warfarin. These are important conditions for ACOs, especially since DOACs are tied to higher patient satisfaction as compared with warfarin. In addition, program incentives found quality measures within VTE and AF can play an important role for both payers and providers. Future costs can also be managed using medication therapy management (MTM) programs. MTM programs are interdisciplinary approaches and when used, can improve monitoring and increase appropriate use of anticoagulants.[5,6]

Importance of Adherence for VTE and AF

As with VKAs, strict adherence to DOACs is critical for treatment and management of VTE and AF. Unfortunately, plasma levels cannot be used to gauge adherence of DOACs, which means that not only is it difficult to monitor patient adherence, but also that these patients do not require as many follow-up visits compared with patients monitored for adherence to VKAs.[117] Data on self-reported adherence to anticoagulation treatment are similar for patients on VKAs and DOACs (56.2% and 57.1%, respectively), with age, female gender, use of additional oral medications, and retirement status as indicators of adherence.[118]

An evaluation of the PharMetrics Integrated Claims database from January 1, 2004 to December 31, 2009 demonstrated that patients with NVAF had a 26% higher likelihood of adherence to treatment regimens for chronic conditions requiring once-daily medications compared with twice-daily regimens. When compliance was calculated by medication possession ratio (MPR), 75.3% of patients on once-daily regimens were adherent to treatment, compared with 70.4% on twice-daily regimens (P <.001). When compliance was calculated by proportion of days covered (PDC), 56.5% of patients were adherent to once-daily regimens at 12 months, compared with 49.6% for twice-daily regimens (P <.001). In both cases, adherence was defined as an MPR or PDC ≥0.8.[119] Thus, once-daily drugs (rivaroxaban and edoxaban) may have advantages over the twice-daily drugs in patients who struggle with adherence of twice-daily drugs (dabigatran and apixaban).

Unfortunately, such low adherence rates may severely diminish the effectiveness of treatment with a DOAC. Data on adherence to DOAC therapy is limited. However, a real-world analysis of adherence during the first year of treatment on dabigatran in a cohort of 2960 Danish patients with newly diagnosed NVAF shows promising results in patients with higher morbidities. In this analysis, adherence was characterized using PDC, gap rates, and restart rates at the end of 1 year of treatment. The overall 1-year PDC was 83.9%, and 76.8% of patients had a 1-year PDC ≥80%. Patients with higher morbidity, including patients with a higher risk of stroke or bleeding, were more adherent to treatment. Overall, patients averaged 1.4 gaps per year, with patients with higher morbidity having more, but shorter, gap periods.[120]

In another real-world study, MPR was calculated over a 1-year period for patients prescribed dabigatran at a large academic medical center who did not use a mail-order pharmacy. The mean MPR in this study was 0.63 (n = 159), with 43% of the patients having an MPR <0.80. In the 57% of patients who participated in the study with an MPR ≥0.80, the mean MPR was 0.94.[121] The relatively low mean MPR seen in this study and the higher

rates of adherence in patients with greater morbidity seen in the Danish study may indicate that adherence improves with more frequent follow-ups or increased frequency of doctor-patient communication. Although half-lives are significantly shorter with the DOACs as compared with warfarin, more data is needed to assess the effects of missed doses on clinical outcomes. While anticoagulation status may be more quickly affected with missed doses of a DOAC, one should not assume that clinical outcomes are different than with missed doses of warfarin, as the effects may just be more latent with warfarin. For ACOs and integrated healthcare systems, it may be beneficial to put resources behind ensuring anticoagulation adherence when possible to minimize thrombotic events. Practical considerations that may improve anticoagulation adherence include[121]:

- Utilizing shared decision making with the patient covering bleeding and thrombotic risks, as well as advantages and disadvantages of varying agent choices.
- Improved patient education on the need for treatment and the importance of treatment adherence, including the involvement of family members and caregivers.
- Increased follow-ups and communication reinforcing adherence by all healthcare professionals involved in the patient's care, including the primary care practitioner, specialists, pharmacists, etc.
- Use of supportive therapies as reminders, including prescription reminders from specialty pharmacies, prescription refill reminder programs, smartphone applications with reminders to take medications, etc.
- Adjustment of treatment regimens to incorporate more once-daily treatments and reduce pill burden.
- Checking anticoagulation refill history via the electronic health record or by calling the patient's pharmacy.

Conclusions

VTE and AF are very distinct conditions; however, they both place patients at risk for a serious thromboembolic event. VKAs, such as warfarin, have been the traditional treatment of choice for VTE and are used to reduce the risk of stroke in patients with AF. While warfarin has been shown to significantly reduce the risk of stroke, it is difficult to manage because it requires frequent laboratory monitoring and has multiple drug-drug and drug-food interactions. Historically, approximately half of patients with AF have not been treated with warfarin and the patients who are on warfarin are poorly controlled with time in therapeutic range of only approximately 50%. This provides a large opportunity for improvement with DOACs to be utilized, especially in rural areas of the United States and other countries where routine monitoring of warfarin is difficult. The acquisition cost of warfarin is significantly less than that of the DOACs. However, given the body of evidence demonstrating the effectiveness and superior safety profile of these new anticoagulants, along with their easy dosing, lack of monitoring, and potential cost-effectiveness in long-term treatment, healthcare providers, ACOs, healthcare systems, and formulary decision makers are given a unique opportunity to use evidence-based clinical care to improve overall patient care and management. Several studies in various arenas are ongoing with current and new DOACs which will make the anticoagulant market even more complex. Thus, there is a significant need to educate all healthcare professionals, including formulary decision makers, in the unique attributes of DOACs, such as their pharmacologic profile, transitions of care throughout healthcare settings with anticoagulants, and the DOACs' role in acute and long-term management of VTE and AF.

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CE POSTTEST QUESTION | Pre-/Post Test Questions

1. **Annually, venous thromboembolism (VTE) and atrial fibrillation (AF) impact up to _____ and _____ American, respectively.**
   A. 3 million; 1 million
   B. 2 million; 6 million
   C. 1 million; 12 million
   D. 4 million; 18 million

2. **Nonadherence to warfarin and direct oral anticoagulants for stroke reduction in nonvalvular atrial fibrillation (NVAF) and VTE treatment would likely _____ clinical effectiveness and _____overall healthcare associated costs.**
   A. Decrease/decrease
   B. Decrease/increase
   C. Not impact/increase
   D. Increase/decrease

3. **In general for stroke reduction in NVAF, direct oral anticoagulants (DOACs) demonstrated _____ and _____ as compared with warfarin**
   A. Better efficacy/worse bleeding profile
   B. Similar or better efficacy/worse bleeding profile
   C. Worse efficacy/better bleeding
   D. Similar or better efficacy/similar or better bleeding profile

4. **In general, DOACs compared with warfarin appear to:**
   A. Have lower drug acquisition costs and demonstrate lower overall healthcare costs
   B. Have higher drug acquisition costs but demonstrate lower overall healthcare costs
   C. Have higher drug acquisition costs and demonstrate higher overall healthcare costs
   D. Have similar drug acquisition costs and demonstrate similar overall healthcare costs

5. **Appropriate hospital VTE prevention programs can:**
   A. Increase prophylaxis rates and significantly reduce hospital-associated VTE, preventable VTE, VTE-associated morbidity, fatal pulmonary embolism (PE), and healthcare costs
   B. Reduce healthcare costs but not have any impact on morbidity and mortality.
   C. Decrease VTE prophylaxis rates and have a negative effect on hospital-associated VTE, preventable VTE, VTE-associated morbidity, and fatal PE, as well as healthcare costs
   D. Have positive effects on prophylaxis rates but no effects on clinical outcomes or costs.

6. **Which of the DOACs has the least renal clearance?**
   A. Dabigatran
   B. Rivaroxaban
   C. Apixaban
   D. Edoxaban

7. **Which of the DOACs should be taken with food to increase absorption at the higher doses of 15 mg and 20 mg?**
   A. Dabigatran
   B. Rivaroxaban
   C. Apixaban
   D. Edoxaban

8. **In the atrial fibrillation trials (RE-LY, ROCKET-AF, ARISTOTLE, and ENGAGE-TIMI 48), which was the only DOAC to demonstrate a significant decrease in ischemic stroke (as opposed to hemorrhagic stroke) compared with warfarin?**
   A. Dabigatran
   B. Rivaroxaban
   C. Apixaban
   D. Edoxaban

9. **In the DOAC VTE trials (RE-COVER, EINSTEIN pooled, AMPLIFY, and Hokusai), the 2 DOACs that had less major bleeding compared with warfarin were:**
   A. Dabigatran and edoxaban
   B. Rivaroxaban and apixaban
   C. Apixaban and edoxaban
   D. Dabigatran and apixaban

10. **Advantages of DOACs compared with warfarin include:**
   A. Lack of routine monitoring as with warfarin, rapid onset and offset with short half-lives, minimal drug-drug and drug-food interactions, improved bleeding profiles, and improved patient quality of life
   B. Ease of reversal
   C. Lack of routine monitoring with slow onsets and slow offsets
   D. Lower overall healthcare and drug acquisition costs, lack of routine monitoring, rapid onset and offset, minimal drug-food interactions, and similar quality of life

Sample Posttest

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