Understanding the New Emerging Oral Anticoagulants for Venous Thromboembolism Prophylaxis

Mary Kay Welle

Patients who have major orthopaedic surgery are at high risk for developing venous thromboembolism (VTE). Assessment of risk and treatment to prevent VTE are considered standard of care due to its significant morbidity, potential mortality, and clinical burden and cost. Guidelines are available aiding orthopaedic surgeons to choose the best methods of VTE prophylaxis. Optimal VTE prevention has not been achieved. Recent advances in the understanding of the coagulation cascade have evolved because of a novel understanding of the molecular influences on the coagulation pathway. Subsequently, new anticoagulants have been developed that target specific factors within the coagulation cascade that are contrasted to the currently used agents that have a broad effect on the coagulation pathway. Multiple clinical trials have tested the new anticoagulants within the orthopaedic total knee and total hip arthroplasty arena. In addition, research to find new ways to prevent VTE was driven by limitations of the currently available agents. The new oral anticoagulants extensively trialed in orthopaedics are dabigatran, rivaroxaban, and apixaban. Clinical trials indicate that the new oral agents have the potential to impact VTE prophylaxis in regard to efficacy, predicta bility and consistency, clinical monitoring, adherence as to use and duration, and convenience. Concerns persist regarding issues of bleeding complications, liver enzyme elevation, patients with renal disease, and drug-to-drug interactions. The new oral agents do not have an antidote to reverse bleeding effect and have no reliable assay to measure effect. Nurses need to be aware of these new VTE prophylactic choices and their implications in order to provide the best outcomes for their patients.

It has been well established that after major orthopaedic surgery, patients are at high risk for developing venous thromboembolism (VTE) and therefore, VTE prophylaxis is considered standard of care (Hou, 2011a; Hull, Yusen, & Bergqvist, 2009). Controversies exist as to the safest and most clinically relevant methods for VTE prevention. Choices of VTE prophylaxis methods are based primarily on risk versus benefit along with considerations of cost and convenience. The primary benefit of thromboprophylaxis is the prevention of deep vein thrombosis (DVT) and subsequent pulmonary embolism (PE; Geerts et al., 2003; Cohen et al., 2003; Heit et al., 1999). The sequelae of long-term complications from a primary DVT pose a substantial economic burden along with decreased quality of life (Hou, 2011b). The economic burden of managing acute and chronic VTE is significant, especially if complications require rehospitalization, prolonged hospital stays, and long-term therapy and monitoring (Hou, 2011b).

VTE Prophylaxis Treatment Choice

Choosing the method of VTE prophylaxis can be complicated. The choice can be difficult because of emerging data, novel techniques, and new discoveries affecting overall VTE risk versus benefit strategy to meet quality measures (Trujillo, 2010). Much has been published regarding VTE prophylactic guidelines and guideline adherence after major orthopaedic surgery because VTE prophylaxis is considered standard of care because there are numerous choices of treatment (Trujillo, 2010). Presently, two guidelines direct orthopaedic surgeons...
regarding VTE prevention modality choice after total hip and total knee arthroplasty and are the American Academy of Orthopaedic Surgeons (AAOS) guidelines published in 2007 and the American College of Chest Physicians (ACCP) guidelines published 25 years ago and updated every 3 years (Eikelboom, Karthikeyan, Fagel, & Hirsh, 2009; Hou, 2011b; Trujillo, 2010). A notable difference between the two guidelines, as stated by Eikelboom et al. (2009), is related to outcome criteria. The ACCP research measured for DVT, both symptomatic and asymptomatic. The AAOS measured outcomes for symptomatic PE and fatal PE. The variant outcome criteria created a major point of disagreement as to whether DVT can be defined as a substitute for PE in measurement of complications (Hou, 2011a). Another very important difference between the two guidelines to orthopaedic surgeons is that the AAOS also considered the effects of anticoagulants for serious joint bleeding and wound drainage (Hou, 2011a).

In regard to adherence to one guideline or the other, a study by Markel et al. (2010) of the American Association of Hip and Knee Surgeons investigated practice patterns of joint arthroplasty surgeons. The authors found through their survey that 74% of the hospitals recognized the ACCP guidelines; however, 68% of the orthopaedic surgeons reported that they preferred to follow the AAOS guidelines for VTE prophylaxis after total hip and knee arthroplasty. Hou (2011a) states that because of increased hospital quality and safety committee regulations, accountability for accreditation, and government groups weighing in, orthopaedic surgeons focus more on absence of VTE as an outcome. Friedman, Gallus, Cusner, FitzGerald, and Anderson (2008) found that adherence to guidelines in regard to start time, duration, and intensity of VTE prophylactic therapy after major orthopaedic surgery is relatively low. Considerable confusion persists regarding guideline utility creating barriers to VTE prophylaxis (Haralson, 2008). Barriers for poor compliance of the ACCP guidelines as outlined by Caprini and Hyers (2006) include lack of familiarity with recommendations, overestimation of bleeding risk, underestimation of thrombotic risk, and system limitations. Friedman (2010) cites that another potential barrier for optimal use of anticoagulants in orthopaedics may be due to inconvenience of use issues for the currently prescribed agents. Also, when considering benefit versus harm, as Trkulja and Kolundzic (2010) state, pivotal efficacy/safety trials of VTE prophylaxis after major orthopaedic surgery are conducted mostly for regulatory purposes and do not include patients who have preexisting risk factors for either VTE or bleeding and therefore do not represent real-life situations. The authors state that the association of DVT and PE in major orthopaedic surgical patients may be weaker than that in other sicker patient populations and that strategies recommended may not fit the orthopaedic patient.

Despite guideline recommendation and system regulations, bleeding risk continues to be a huge concern among orthopaedic surgeons when considering treatment with an anticoagulant to prevent VTE. Both Friedman (2010) and Hou (2011a) have identified that postoperative bleeding complication is the number 1 risk that orthopaedic surgeons regard when choosing prophylactic VTE protection. In regard to the specific issue of bleeding, Deitelzweig et al. (2008) relay that orthopaedic surgeons regard bleeding at the surgical site and within the replaced joint space as the top bleeding concerns. Levy, Key, and Azran (2010) acknowledge that anticoagulants may potentiate bleeding so it is important for surgeons to understand the implications. In addition, concern about bleeding is warranted as bleeding caused by perioperative antithrombotic agents can pose a serious risk for those patients receiving neuroaxial anesthesia as the risk of a spinal hematoma is increased 15 times when anticoagulants are not used with precaution (Rosencher, Bonnet, & Sessler, 2007). The development of a spinal hematoma can lead to permanent paralysis (Levy et al., 2010). Because of the limited awareness of the true burden of VTE combined with the fear of bleeding, the use of thromboprophylaxis has been suboptimal in orthopaedic surgical patients (Friedman et al., 2008). In response to the bleeding risk, Dahl and Bergqvist (2002) relay that in the United States, some surgeons are more concerned about bleeding than thromboprophylaxis. In addition, according to the authors, to further confuse the issue of bleeding risk, international standards surgeons are lacking on how to measure perioperative bleeding and bleeding related to the use of anticoagulants. Interpretations of bleeding complications are problematic because of the wide range of major bleeding definitions in studies, which make it difficult to compare risk. Specific to this problem, Hull et al. (2009) state that there are 10 different terms in the literature to describe bleeding events. Also, studies do not report bleeding events that are of relevance to orthopaedic surgeons (Hull et al., 2009).

Several regulatory agencies, government offices, and consumer groups have mandated VTE prophylaxis for hospitalized patients. In 2008, the Centers for Medicare & Medicaid Services declared VTE after surgery a never event and will no longer reimburse costs associated with the subsequent hospital-acquired complications (Hou, 2011b). In addition, The Surgical Care Improvement Project was initiated in 2006 with the overall goal, by 2010, to reduce the incidence of VTE in surgical patients by 25% (Hou, 2011b).

**Shortcomings of the Currently Used Agents**

Pharmacologic VTE prophylactic agents that are currently used have been proven to be efficacious in orthopaedics in the United States. These include the following: an oral vitamin K antagonist (VKA) as warfarin; the low-molecular-weight heparins (LMWH) as enoxaparin, dalteparin, and tinzaparin; and the synthetic pentasaccharide as fondaparinux (Geerts et al., 2008; Lassen & Laux, 2008). In 2003, the Food and Drug Administration (FDA) approved desirudin, a direct thrombin inhibitor that requires administration as a subcutaneous injection for the prevention of VTE in major orthopaedic procedures. Desirudin provides another option as an injectable. Neither the ACCP guideline nor the AAOS guideline includes the use of desirudin as a choice for...
VTE prophylaxis following total knee or total hip arthroplasty (Eikelboom et al., 2009).

Vitamin K antagonist has been used as the major anticoagulation agent for nearly 60 years, and warfarin has been the only oral VKA agent available in the United States (Friedman, 2010). Warfarin was approved for clinical use in 1954 and has since become one of the most prescribed drugs in the world (Mazza & Yale, 2009). Unfractionated heparins were developed more than 70 years ago and LMWH were developed in the 1980s (Hirsh, O’Donnell, & Eikelboom, 2007). Fondaparinux, as a synthetic pentasaccharide, was approved for use in the United States in 2001 (Lassen & Laux, 2008).

The current-generation thromboprophylactic agents have been identified not only as being efficacious, having good benefit to risk ratios, but also as having significant drawbacks (Geerts et al., 2008). Additional issues with the currently used anticoagulants are that they require therapeutic management and monitoring. In regard to monitoring the effects of warfarin, a study by Ansell et al. (2008) demonstrated that less than 50% of patients using warfarin are within the international normalized ratio (INR) therapeutic range of 2–3 placing many patients at risk for bleeding or thrombosis, depending on the INR level. Although the study by Ansell et al. involved patients who were on warfarin for the long term to treat a chronic cardiovascular condition, it demonstrates the need for novel oral anticoagulants that are free of frequent monitoring or dose adjustment requirements. For those treated with warfarin outside the therapeutic range, genetic variability was cited as the reason for the undesired INR results (Mazza & Yale, 2009). For a comprehensive list of the limitations and clinical impact of the common currently used anticoagulants used in orthopaedics, refer to Table 1.

The New Oral Anticoagulant Targets on the Coagulation Cascade

Concepts regarding thrombi creation are complex. New understandings are emerging and evolving. Modern theories of blood coagulation began in the 1940s (Riddel, Aouizerat, Miaskowski, & Lillicrap, 2007). Comprehension of blood coagulation has recently rapidly evolved because of new insight into the understanding of the molecular orchestration of coagulation, isolation and characteristics of antithrombotic proteins, and advances in recombinant DNA technology (Eriksson & Quinlan, 2006; Weitz, Hirsh, &

<table>
<thead>
<tr>
<th>Drug Classification</th>
<th>Limitation</th>
<th>Clinical Implication</th>
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<tbody>
<tr>
<td>Oral VKAs (Warfarin)</td>
<td>Slow onset of action and lengthy half-life</td>
<td>Bridge with rapid-acting anticoagulant until therapeutic INR is achieved</td>
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<tr>
<td></td>
<td>Variability to individual response</td>
<td>Individualize dosing due to common genetic polymorphisms influencing metabolism</td>
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<td></td>
<td>Narrow therapeutic window</td>
<td>Routine monitoring required for overanticoagulation = risk for bleeding, and underanticoagulation = risk for thrombosis</td>
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<td></td>
<td>Need for serum INR laboratory monitoring</td>
<td>Monitor at least 1 x per week is inconvenient, requires monitoring and response, costly</td>
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<td></td>
<td>Numerous food–drug interactions</td>
<td>Dietary counseling, medication analysis, and monitoring</td>
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<td></td>
<td>Vitamin K–dependent protein synthesis reduction</td>
<td>Risk for skin issues for protein C– or protein S–deficient patients, increased risk for osteoporosis</td>
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<td></td>
<td>Difficult to manage periprocedural treatments</td>
<td>High risk for injury, blood loss, need to lower INR below therapeutic levels prior to procedure, often labor-intensive and delay of procedure</td>
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<tr>
<td></td>
<td>Underutilization due to complexity of use and adverse side effects</td>
<td>Need for careful monitoring, follow-up, ongoing education</td>
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<td></td>
<td>Risk for thrombocytopenia</td>
<td>Risk not as high as with heparin, higher risk with enoxaparin and almost nonexistent with fondaparinux</td>
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<tr>
<td>Enoxaparin (LMWH) and synthetic pentasaccharide (fondaparinux) and direct thrombin inhibitor (desirudin)</td>
<td>Lack of an antidote</td>
<td>Protamine sulfate only partially neutralizes enoxaparin. Has no effect on fondaparinux due to long half-life</td>
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<td></td>
<td>Potential for accumulation in renal impaired patients</td>
<td>Assess renal function before prescribing and monitor; dose adjustment with enoxaparin and desirudin; contraindicated with fondaparinux, lack of data for dalteparin</td>
</tr>
<tr>
<td></td>
<td>Contraindicated for weight &lt;50 kg for fondaparinux</td>
<td>Weight monitoring necessary</td>
</tr>
<tr>
<td></td>
<td>Affect platelet count</td>
<td>Serum laboratory assessment and monitoring</td>
</tr>
<tr>
<td></td>
<td>Need for daily subcutaneous injections</td>
<td>May need skilled nursing care for injection, inconvenient, long-term use limitations</td>
</tr>
</tbody>
</table>

Coagulation factors, as discovered, were designated by roman numerals. The numeric system of numbering is not representative of a relationship between factors but is based on the timing and sequence of discovery. Within the system of coagulation numeration, the suffix “a” indicates the activated form (Riddel et al., 2007).

The development of the new oral anticoagulants stems from discoveries of small molecule inhibitor coagulation enzymes. These new discoveries have been described as blockers of specific coagulation enzymes at their catalytic pocket that led to the formulation of the new anticoagulants (Zikria, Ansell, & Ansell, 2009).

The major difference of these new oral anticoagulants is the mechanism of action and how they are metabolized (Ansell, 2007; Friedman, 2010). Vitamin K antagonists or heparin-related compounds have a broad effect on multiple coagulation factors. In contrast, the new anticoagulants directly target and neutralize a specific coagulation factor. To alleviate some of the unpredictable behavior and the broad effect of VKAs and unfractionated heparins, recent research has focused on the single coagulation factors, namely thrombin (IIa) and factor Xa (Ansell, 2007). The thrombin and factor Xa inhibitors are the most advanced in clinical development (Sattari & Lowenthal, 2010). Each of the new oral anticoagulants selectively inhibits central coagulation protein enzymes (Steffel & Lüscher, 2009). Simply explained, within the coagulation cascade, the contact pathway (intrinsic pathway) and the tissue factor pathway (extrinsic pathway) combine to activate thrombus formation. When the two pathways converge, it leads to the formation of factor Xa, transforming prothrombin to thrombin, which then activates the final common pathway. The final common pathway ultimately leads to the formation of fibrin and insoluble fibrin (Riddel et al., 2007). Development of the new anticoagulants followed the logic that inhibition of any enzyme within the coagulation cascade should potentially reduce the formation of a clot (Riddel et al., 2007). Refer to Figure 1 for sites of action of the new factor IIa and Xa inhibitors.

Clinical Development and Clinical Trials of the New Oral Anticoagulants

The three new oral anticoagulants that have been clinically trialed to prevent VTE after major orthopaedic surgery are dabigatran, rivaroxaban, and apixaban. These novel agents are direct and specific target inhibitors of thrombin (IIa) or factor Xa.

Because of the morbidity and mortality associated with VTE and because it is considered to be preventable after surgery, massive research has been conducted into the pathogenesis of thrombotic disease leading to the discovery of new oral anticoagulants (Tsiara, Pappas, Boutis, & Laffan, 2011). Two general reasons for the development of the new anticoagulants include (1) alleviating concerns regarding the risk–benefit ratio and (2) reducing inconvenience and limitations of the currently used agents (Weitz et al., 2008). They were also developed to ensure that they would be at least as effective and that they would pose as equal or less of a risk for bleeding as the VKAs and heparins (Wietz et al., 2008). Some of the desirable characteristics of the new agents, as noted in the literature, include that they (1) are administered in fixed doses because of predictable pharmacokinetics, (2)
do not need a bridge of rapid-acting parenteral anticoagulant as they have a rapid onset of action, (3) do not require serum laboratory monitoring, and (4) have few drug–drug and drug–food interactions (Weitz et al., 2008; Zikria et al., 2009). For more specific characteristics of an ideal anticoagulant as they have a rapid onset of action, (3) do not require serum laboratory monitoring, and (4) have few drug–drug and drug–food interactions (Weitz et al., 2008; Zikria et al., 2009). For more specific characteristics of an ideal anticoagulant, refer to Table 2.

Orthopaedics has been the testing ground for the development of these new anticoagulants. Researchers have established that orthopaedic patients are at high risk for VTE without antithrombotic treatment and are a well-defined group (Geerts et al., 2008). In addition, the elective nature of major orthopaedic surgery assists with protocol adherence. Patients are usually medically optimized and therefore survive the surgery. Moreover, there are specific, defined outcomes for both efficacy and safety of treatment (Eriksson & Dahl, 2004; Eriksson & Quinlan, 2006). Research is also robust regarding antithrombotic medication within the orthopaedic perioperative period due to the large volume of major orthopaedic surgeries. Kurtz et al. (2005) share that in 2005, there were approximately 250,000 THRs, and they estimate that by 2030, the number will increase by 174% to 572,000. Also, unlike chronic medical conditions that require a lifetime of antithrombotic treatment, the research timeline in orthopaedics is more manageable.

Ximelagatran, a direct thrombin inhibitor, was the first oral drug developed in the new class of anticoagulants (Vaughn, 2005). It was trialed in comparison with warfarin and enoxaparin and was initially approved for use by the European Medicines Agency based on trial results in orthopaedic total joint arthroplasty (Hou, 2011a). It held promise as the initial results, indicating that it was at least as effective as warfarin and enoxaparin. However, long-term use demonstrated that ximelagatran was associated with hepatotoxicity and failed the FDA approval (Merli, Spyropoulos, & Caprini, 2009).

Besides dabigatran, rivaroxaban, and apixaban, there are many other new oral anticoagulants in clinical trials and in development. Dabigatran, rivaroxaban, and apixaban have received the most attention due to the extensive nature of their clinical trials (Trujillo, 2010). Numerous trials, most with large sample sizes, have been conducted testing dabigatran, rivaroxaban, and apixaban, all comparing the new agents against enoxaparin after total hip and total knee arthroplasty in both the United States and Europe during the years 2000–2010. Each of these new agents has been studied in Phase III trials. According to Halperin (2009), the FDA and the European Medicines Agency regulate the guidance for the development, design, and evaluation of the trials. Both agencies base their approval decisions on the results of the Phase III trials. According to U.S. National Institutes for Health (2011), in Phase III trials, the number of subjects ranges from 1,000 to 3,000. Trial purposes were to confirm effectiveness, monitor for side effects, make comparisons to commonly used treatments, and ensure safety during the trials (Halperin, 2009).

Dabigatran, marketed as Pradaxa, has been approved for use in the United States by the FDA in October 2010 for patients with nonvalvular atrial fibrillation (U.S. Department of Health and Human Services, 2010). Dabigatran was approved in the European Union in April 2008 and in Canada in June 2008 for patients undergoing total knee and THR surgery (Hou, 2011a, 2011b). As recently as of July 1, 2011, the FDA has approved rivaroxaban, marketed as Xarelto, to be used for total hip and knee VTE prophylaxis (U.S. Department of Health Human Services, 2011a). The use of rivaroxaban was approved for the same indication in both the Canada and the European Union in 2008 (Hou, 2011a, 2011b). Apixaban has not been approved for use for any indication or in any country thus far (Hou, 2011a, 2011b).

For details of the names of the Phase III trials for dabigatran, rivaroxaban, and apixaban, refer to Table 3. All Phase III trials researched the new oral anticoagulants against enoxaparin after major orthopaedic surgery and measured for composite VTE. There were two separate primary outcomes for the phase III trials. One was primary efficacy measured as composite VTE and all cause mortality. The other outcome was primary safety measured as major bleeding, although bleeding definitions varied somewhat among trials (Trujillo, 2010; Ufer, 2010). Length of treatment and dosage of enoxaparin varied between the trials on the basis of the type of major orthopaedic surgery. Trials also varied according to regimen recommendations for location of either Europe or the United States, dependent on the type of surgery (Trujillo, 2010).

**Summaries of the Phase III Trials: Primary Efficacy and Primary Safety Outcomes**

When data from the Phase III trials were studied separately and as pooled results, conclusions varied somewhat...
by the reviewers. This may be due to the assorted dose and length of treatment of comparative enoxaparin in the trials against a fixed dose and fixed length of treatment of the new oral anticoagulant and the type of surgery either total knee or total hip arthroplasty. Not all definitions of outcome measurement criteria were the same across all Phase III trials. According to Ageno (2009), the definition of bleeding in the RECORD trials differed for the other new oral anticoagulant Phase III trials. Ageno advises that indirect comparisons on safety profiles of the new anticoagulants must be considered cautiously.

Friedman et al. (2010) conducted a pooled analysis for the efficacy and safety of dabigatran in the RE-MOBILIZE, RE-MODEL, and RE-NOVATE Phase III trials after total hip and knee arthroplasty, and concluded that dabigatran is very similar to enoxaparin, represents a good oral alternative, and had no clinical significant difference related to mortality or for safety. When these same dabigatran trials were examined separately, Trujillo (2011) relays that in the RE-MOBIZE trial, dabigatran was shown to be inferior to enoxaparin for VTE protection.

In regard to rivaroxaban, Agneo (2009) found that rivaroxaban was superior to enoxaparin for VTE prophylaxis and has a similar safety profile for all RECORD trials. Ufer (2010) indicates that among all of the RECORD trial results, incidence of major bleeding was not significantly different between the rivaroxaban and

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study Drug and Dose vs Control Drug and Dose</th>
<th>Indication; Sample; Duration</th>
<th>VTE/Mortality Efficacy Outcome Results Study vs Control</th>
<th>Bleeding Safety Outcome Results Study vs Control</th>
<th>Published Results Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renovate</td>
<td>Dabigatran 150 mg 1× day or 220 mg 1× day vs enoxaparin 40 mg 1× day</td>
<td>THA; N = 3,494; 28–25 days</td>
<td>8.6% (dabigatran 150 mg), p ≤ .001 6.0% (dabigatran 220 mg), p ≤ .001 vs 6.7% (enoxaparin 40 mg)</td>
<td>1.3% (dabigatran 150 mg), p = .60 2.0% (dabigatran 220 mg), p = .44 vs 1.4% (enoxaparin 40 mg)</td>
<td>Eriksson et al. (2007b)</td>
</tr>
<tr>
<td>Remodel</td>
<td>Dabigatran 150 mg 1× day or 220 mg 1× day vs enoxaparin 40 mg 1× day</td>
<td>TKA; N = 2,101; 6–10 days</td>
<td>40.5% (dabigatran 150 mg), p = .017 36.4% (dabigatran 220 mg), p = .0003 vs 37.7% (enoxaparin 40 mg)</td>
<td>1.3% (dabigatran 150 mg), p = 1.0 1.5% (dabigatran 220 mg), p = .82 vs 1.3% (enoxaparin 40 mg)</td>
<td>Eriksson et al. (2007a)</td>
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<tr>
<td>Remobilize</td>
<td>Dabigatran 150 mg 1× day or 220 mg 1× day vs enoxaparin 30 mg 2× day</td>
<td>TKA; N = 2,615; 12–15 days</td>
<td>33.7% (dabigatran 150 mg), p ≤ .001 31.1% (dabigatran 220 mg), p = .02 vs 25.3% (enoxaparin 30 mg)</td>
<td>1.3% (dabigatran 150 mg), no p value 1.5% (dabigatran 220 mg), no p value vs 1.3% (enoxaparin 30 mg)</td>
<td>Ginsberg et al. (2009)</td>
</tr>
<tr>
<td>Record 1</td>
<td>Rivaroxaban 10 mg 1× d vs enoxaparin 40 mg 1× d</td>
<td>THA; N = 4,541; 31–39 d</td>
<td>1.1% (rivaroxaban 10 mg), p ≤ .001 3.7% (enoxaparin 40 mg)</td>
<td>0.3% (rivaroxaban 10 mg), p = .94 vs 0.1% (enoxaparin 40 mg)</td>
<td>Eriksson et al. (2008)</td>
</tr>
<tr>
<td>Record 2</td>
<td>Rivaroxaban 10 mg 1× day vs enoxaparin 40 mg 1× day</td>
<td>THA; N = 2,509; 31–39 days</td>
<td>2.0% (rivaroxaban 10 mg), p ≤ .0001 vs 9.3% (enoxaparin 40 mg)</td>
<td>&lt;0.1% (rivaroxaban 10 mg), p = .25 vs &lt;0.1% (enoxaparin 40 mg)</td>
<td>Kakkar et al. (2008)</td>
</tr>
<tr>
<td>Record 3</td>
<td>Rivaroxaban 10 mg 1× day vs enoxaparin 40 mg 1× day</td>
<td>THA; N = 2,531; 10–14 days</td>
<td>9.6% (rivaroxaban 10 mg), p ≤ .001 18.9% (enoxaparin 40 mg)</td>
<td>0.6% (rivaroxaban 10 mg), p = .93 vs 0.5% (enoxaparin 40 mg)</td>
<td>Lassen et al. (2008)</td>
</tr>
<tr>
<td>Record 4</td>
<td>Rivaroxaban 10 mg 1× day vs Enoxaparin 30 mg 1× day</td>
<td>THA; N = 3,148; 10–14 days</td>
<td>6.9% (rivaroxaban 10 mg), p = .0118 vs 10.1% (enoxaparin 30 mg)</td>
<td>0.7% (rivaroxaban 10 mg), p = .106 vs 0.3% (enoxaparin 30 mg)</td>
<td>Turpie et al. (2009)</td>
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<tr>
<td>Advance 1</td>
<td>Apixaban 2.5 mg 2× day vs enoxaparin 30 mg 2× day</td>
<td>TKA; N = 3,195; 10–14 days</td>
<td>9.0% (apixaban 2.5 mg), p = .06 vs 8.8% (enoxaparin 30 mg)</td>
<td>0.7% (apixaban 2.5 mg), p = .053 vs 1.4% (enoxaparin 30 mg)</td>
<td>Lassen et al. (2009)</td>
</tr>
<tr>
<td>Advance 2</td>
<td>Apixaban 2.5 mg 2× day vs enoxaparin 40 mg 1× day</td>
<td>TKA; N = 3,057; 10–14 days</td>
<td>15.06% (apixaban 2.5 mg), p ≤ .0001 vs 24.37% (enoxaparin 40 mg)</td>
<td>0.6% (apixaban 2.5 mg), p = .3014 vs 0.9% (enoxaparin 40 mg)</td>
<td>Lassen et al. (2010b)</td>
</tr>
<tr>
<td>Advance 3</td>
<td>Apixaban 2.5 mg 2× day vs enoxaparin 40 mg 1× day</td>
<td>TKA; N = 5,407; 32–38 days</td>
<td>1.4% (apixaban 2.5 mg), p ≤ .001 vs 3.9% enoxaparin</td>
<td>0.8% (apixaban 2.5 mg), no p value vs 0.7% (enoxaparin 40 mg)</td>
<td>Lassen et al. (2010a)</td>
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Note. All tested for primary efficacy outcome as composite VTE and all-cause mortality during treatment and for safety outcome as incidence of major bleeding. THA = total hip arthroplasty; TKA = total knee arthroplasty; VTE = venous thromboembolism.
enoxaparin. However, Van Theil et al. (2009), in pooled data from all the RECORD trials, concluded that there was a clear and consistent trend for increased major bleeding with rivaroxaban.

Apixaban was compared with enoxaparin in the ADVANCE 1, 2, and 3 Phase III trials. The results for VTE protection were varied and attributed to the altered doses of enoxaparin in the ADVANCE trials (Trujillo, 2011; Ufer, 2010). In regard to incidence of major bleeding with apixaban, lower bleeding rates were reported for the apixaban group in the ADVANCE 1 trial, nominally lower rates in the ADVANCE 2 trial, and similar rates for ADVANCE 3 trial (Ufer, 2010). There were no pooled studies of the ADVANCE trials.

PHARMACODYNAMICS AND PHARMACOKINETICS

Dabigatran: Direct Thrombin Inhibitor

The direct thrombin inhibitors are also referred to as factor IIa inhibitors. Thrombin plays a complex role in the coagulation cascade by cleaving fibrinogen to form a fibrin mesh and a clot. The direct thrombin inhibitors inhibit the enzymatic activity of thrombin and inhibit fibrin-bound thrombin, preventing clot formation (Mazza & Yale, 2009). Dabigatran prolongs coagulation formation through thrombin inhibition, is specific for thrombin, and has little effect on other coagulation factors (Eriksson, Quinlan, & Weitz, 2009).

Dabigatran etexilate is a prodrug that is rapidly converted into dabigatran, which is a potent, nonpeptidic small molecule. It directly inhibits both free and clot bound thrombin (Eriksson et al., 2009). Dabigatran was developed as a prodrug type to facilitate gastrointestinal absorption (Eriksson et al., 2009). A prodrug is the inactive form of a drug that is metabolically converted within the body to the active form of the drug. Although the prodrug dabigatran etexilate is rapidly absorbed, it has low oral bioavailability of approximately 7.2% (Blech, Ebner, Ludwig-Schwellinger, Stangier, & Roth, 2008). Peak plasma concentrations after administration occur in about 1.5 hours and steady levels are reached within 3 days of multiple dosing (Stangier, 2008). The average half-life is about 8 hours (Blech et al., 2008). The primary site of metabolism of dabigatran occurs in the liver (Tsiara et al., 2011) with 85% excreted in the urine and 6% in feces (Blech et al., 2008). In Canada and Europe, dabigatran is contraindicated for patients with severe renal failure as defined since creatinine clearance (CrCl) of less than 30 mL/min with a modified dose recommended in patients with decreased CrCl (Eriksson et al., 2007a). According to Tsiara et al. (2011), patients with severe renal failure were not included in the trials for dabigatran. However, there are data from a non-thoropaedic RE-LY trial, indicating that dabigatran is safe for those patients with moderate renal insufficiency, as defined as CrCl of 30–50 mL/min (Eriksson & Friedman, 2009). For patients who are older than 75 years and those with moderate renal failure, it is recommended that the lower dose of dabigatran (150 mg) be administered starting with a half dose the day of surgery (Eriksson & Friedman, 2009). There are no data regarding hepatic toxicity, as patients with severe liver disease have also not been included in the dabigatran trials (Sattari & Lowenthal, 2010). Dabigatran is best absorbed, regardless of food intake, as it contains an acidifying compound to facilitate absorption (Tsiara et al., 2011).

Rivaroxaban and Apixaban: Factor Xa Inhibitors

Factor Xa is uniquely positioned on the coagulation cascade as a connection between extrinsic and intrinsic pathways (Bauer, 2008; Ma, 2007). Factor Xa regulates the creation of thrombin by binding to Factor Va, triggering activation of prothrombin to thrombin formation (Ma, 2007; Mazza & Yale, 2009). Thrombin formation leads to the conversion of fibrinogen to fibrin (Sattari & Lowenthal, 2010). Rivaroxaban and apixaban bind directly to the active Factor Xa site and block chemical interaction with the substrate (Eriksson et al., 2009).

Factor Xa inhibitors are divided into direct and indirect inhibitors. Rivaroxaban is a direct factor inhibitor that interrupts both the intrinsic and extrinsic pathways of the coagulation cascade and inhibits both thrombin formation and the development of clots (Steffel & Lüscher, 2009). Rivaroxaban is available in the active form. The oral bioavailability of rivaroxaban is 80%–100% (Lang, Freudenberger, & Weinz, 2009). Rivaroxaban is metabolized mainly within the liver with the kidneys excreting two thirds of rivaroxaban and the remainder excreted within the feces (Karthikeyan et al., 2009; Walenga & Adiguzel, 2010). Like dabigatran, CrCl must be considered as rivaroxaban is contraindicated in patients with severe renal impairment and must be carefully monitored in patients with renal insufficiency (Eriksson et al., 2009). In addition, as rivaroxaban is mainly metabolized in the liver; it is also recommended that it be contraindicated in patients with severe hepatic disease (Eriksson et al., 2009). Rivaroxaban bioavailability is unaffected by food (Karthikeyan et al., 2009); however, rivaroxaban is best absorbed at least 2 hours after a meal (Tsiara et al., 2011).

Apixaban is available in the active form of the drug. Oral bioavailability is approximately 68% with an absorption rate of 1 hour after administration (Raghavan et al., 2009). Peak plasma levels reached within 2–4 hours (Gross & Weitz, 2008). Half-life ranges between 5 and 13 hours, depending on age and renal clearance status (Eriksson et al., 2009). Rivaroxaban is metabolized mainly within the liver with the kidneys excreting two thirds of rivaroxaban and the remainder excreted within the feces (Karthikeyan et al., 2009; Walenga & Adiguzel, 2010). Like dabigatran, CrCl must be considered as rivaroxaban is contraindicated in patients with severe renal impairment and must be carefully monitored in patients with renal insufficiency (Eriksson et al., 2009). Rivaroxaban bioavailability is unaffected by food (Karthikeyan et al., 2009); however, rivaroxaban is best absorbed at least 2 hours after a meal (Tsiara et al., 2011).

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Drug and Food Interactions of the New Oral Anticoagulants

It is well known that warfarin has numerous drug and food interactions. Patient monitoring and education are necessary to safely treat with this anticoagulant. Multiple drug and food interactions with warfarin are due to hepatic metabolism and with CYP450 enzymatic
mediation (Ansell et al., 2008). Although drug and food interactions are deemed to be less than with warfarin, the new oral anticoagulants target specific enzymes within the coagulation cascade and require careful drug and food interaction consideration that are affected by those specific enzymatic influences (Ansell et al., 2008).

Dabigatran specifically inhibits P-glycoprotein transport (P-gp; Tsiara et al., 2011). Any other drug that affects P-gp can impact drug–drug interactions. The drugs that are contraindicated concurrently with dabigatran are quinidine, verapamil, and clarithromycin (Hou, 2011a; Tsiara et al., 2011). Quinidine doubles the concentration of dabigatran (Hou, 2011a). Dose reduction is advised for amiodarone when used along with dabigatran. In addition, rifampin and St. John’s wort are to be used with caution (Hou, 2011a). It is also advised not to use nonsteroidal anti-inflammatory agents (NSAIDS) or aspirin in conjunction with dabigatran due to an increased risk of bleeding (Hou, 2011a). The bioavailability of dabigatran decreases when administered with the proton pump inhibitors, as dabigatran’s solubility is dependent on an acid environment of pH < 4 (Walenga & Adiguzel, 2010).

Rivaroxaban is metabolized mainly in the liver via CYP3A4/3A5 and CYP2J2 enzymatic activity (Hou, 2011b; Walenga & Adiguzel, 2010). Like dabigatran, it is also affected by P-gp (Hou, 2011a). The CYP3A4 and P-gp inhibitors that increase rivaroxaban’s efficiency and therefore increase bleeding risk are ketoconazole, itraconazole, voriconazole, posaconazole, ritonavir, clarithromycin, erythromycin, lopinavir, indinavir, and conivaptan (U.S. Department of Health and Human Services, Food and Drug Administration, 2011b; Walenga & Adiguzel, 2010). Concurrent drugs that potentiate CYP3A4 and P-gp activity and therefore decrease rivaroxaban’s efficiency are rifampicin, carbamazepine, phenytoin, and St. John’s wort (U.S. Department of Health and Human Services, Food and Drug Administration, 2011b; Walenga & Adiguzel, 2010).

Uses of NSAIDS, anticoagulants, and clopidogrel are also cautioned because of an increase in bleeding risk (U.S. Department of Health and Human Services, Food and Drug Administration, 2011b; Walenga & Adiguzel, 2010). Bleeding risks were noted to increase with the use of opioids or statins in the RECORD rivaroxaban trials but those results were not statistically significant (Hou, 2011a). However, pooled data from the RECORD trials showed no increase in bleeding when rivaroxaban was coadministered with aspirin or with NSAIDS (Walenga & Adiguzel, 2010). For a detailed list of considerations when prescribing and administering rivaroxaban, refer to Table 4.

Apixaban like rivaroxaban is mediated by CYP3A4 enzymatic activity (Walenga & Adiguzel, 2010). Specific drug interactions with apixaban have not yet identified. However, like rivaroxaban and CYP3A4 metabolism influences, the list of contraindicated drugs will most likely include the same drugs that affect rivaroxaban (Walenga & Adiguzel, 2010).

In addition to prescription drug interactions, over-the-counter medications and dietary supplements also have the potential for interactions with the new oral anticoagulants. Careful assessment of prescription medications, over-the-counter medications, and dietary supplements need to be considered, as use of one or more agents concurrently with prescription medication is common. Qato et al. (2008) found, in their study of older adults aged 57–85 years, that 81% used at least 1 prescription medication, 42% used an over-the-counter medication, and 49% used a dietary supplement. Some of the dietary supplements have shown to increase bleeding tendencies such as garlic, the Chinese herb danshen, and vitamin E (Walenga & Adiguzel, 2010).

Generally, noted food interactions with the new oral anticoagulants are few according to Walenga and Adiguzel (2010). This is a welcome change from the numerous food interactions that need to be considered with warfarin administration. Also, gastrointestinal function should be considered as gastric pH, and intestinal motility and binding can affect absorption and elimination of these new oral anticoagulants (Walenga & Adiguzel, 2010). For a general comparison of the new anticoagulants, refer to Table 5.

**Antidotes for the New Oral Anticoagulants**

Currently there are no specific antidotes to stem bleeding after administration of the new oral anticoagulants (Tsiara et al., 2011). According to Tsiara et al. (2011), both warfarin and LMWH have an antidote to reverse anticoagulation activity. Vitamin K specifically and effectively reverses the anticoagulation effect of warfarin (Tsiara et al., 2011). They state that protamine sulfate partially reverses anticoagulation activity of LMWH and that fresh-frozen plasma or recombinant factor VII may also be used to reverse anticoagulant effect of LMWH. Prothrombin complex and recombinant factor FVIIa are being studied as possible reversal agents for the new oral anticoagulants but have no sufficient evidence that they can stop bleeding if necessary (Tsiara et al., 2011). The new compounds that are being researched to reverse the effects of the new anticoagulants are agents with desmopressin and/or antifibrinolytic activity (Tsiara et al., 2011).

**Laboratory Monitoring**

One of the ideal properties of the new oral anticoagulants is that they eliminate the need for laboratory monitoring. Tsiara et al. (2011) caution that monitoring may still be necessary in certain clinical conditions. The authors advise that despite the lack of required laboratory monitoring, clinical supervision remains necessary and includes the following situations: compliance checks with therapy, monitoring the efficacy and possible overtreatment especially for those with renal or hepatic disease, identification and assessing other concurrent drugs that may affect anticoagulation, the assessment and monitoring for the presence of thrombotic disease and/or treatment failure, assessment and monitoring for severe bleeding complications, and identification of those who are surgical candidates to continue with anticoagulation adequacy if essential.

To measure serum laboratory values, new assays need to be developed for the new anticoagulants. According to...
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Plants, Wolowacz et al. (2009) found that dabigatran was
In regard to the cost–benefit of the new oral anticoagulants,
According to the authors, thrombin time and ecarin clotting time are currently the most sensitive available tests for monitoring the effects of dabigatran and the anti-FXa assay is the most sensitive for rivaroxaban.

### COST COMPARISONS

In regard to the cost–benefit of the new oral anticoagulants, Wolowacz et al. (2009) found that dabigatran was more cost-effective than enoxaparin when administered for patients following total knee and total hip arthroplasty surgery and held true even when patients concurrently injected themselves with enoxaparin for the short term. When using dabigatran for more than 30 days, dabigatran was not found to be as cost-effective as enoxaparin. In another study examining cost, McCullagh, Tilson, Walsh, and Barry (2009) compared rivaroxaban against both dabigatran and enoxaparin for cost-effectiveness after total knee and hip arthroplasty. Rivaroxaban was found to be more cost-effective than dabigatran and enoxaparin. There have been no

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studies comparing cost of the new anticoagulants to warfarin. When considering the cost of INR monitoring necessary with warfarin therapy, it is estimated that the new oral anticoagulants will not be as cost-effective as warfarin (Tsiara et al., 2011).

Summary

Major orthopaedic surgical patients are at high risk for the development of VTE. Current VTE prophylactic methods within the orthopaedic arena have been proven to be efficacious. However, there are some safety and use inconvenience issues associated with the currently used agents. Orthopaedic surgeons base their choice of VTE prophylactic agents following major orthopaedic surgery on guidelines by the ACCP or the AAOS. Modality choice is determined by the risk–benefit ratio, which can be difficult to interpret because of varying definitions and varying outcomes measured between the guidelines. The main safety outcome that orthopaedic surgeons consider is bleeding at the surgical incision or within the joint space after major orthopaedic surgery.

The new oral anticoagulants, dabigatran, rivaroxaban, and apixaban, were developed as specific coagulation cascade target inhibitors and tested after total hip and knee arthroplasty in Phase III trials comparing them to warfarin (Tsiara et al., 2011). As specific inhibitors, they eliminate the broad effect of the currently used agents, especially warfarin. The new oral anticoagulants have demonstrated several advantages, including rapid onset of action, predictable properties, and fixed dose prescription. These drugs also do not require laboratory monitoring. Dabigatran and rivaroxaban have been deemed to be efficacious and safe for orthopaedic indications, as they have been approved for orthopaedic use in Europe and in Canada. Currently, rivaroxaban is the only new oral anticoagulant that has been approved by the FDA for use in orthopaedics within the United States. The FDA has approved dabigatran for cardiac indications for those patients with atrial fibrillation. Although tested in trials similar to dabigatran and rivaroxaban, apixaban has not been approved in any country or for any indication.

Concerns persist regarding the new oral anticoagulants with specific issues involved in treating those with renal and hepatic toxicity. In those patients with liver disease, it is advised that all the new oral anticoagulants be administered with caution and close monitoring be performed (Walenga & Adiguzel, 2010). Liver disease can have a marked effect on individual response to anticoagulation. Dabigatran and rivaroxaban are contraindicated in those with severe renal failure as the majority of the drug in both is excreted by the renal system (Hou, 2011a). The impact of hepatic and renal disease, and the effect of drug metabolism, must be taken into serious consideration especially when treating the older adults with the new anticoagulants (Hou, 2011a; Walenga & Adiguzel, 2010). Further research will undoubtedly follow as ximelagatran was removed from the European and Canadian markets soon after its release due to hepatic toxicity. More studies regarding complications and safety need to be conducted.

Concurrent use of other medications that affect CYP3A4 and P-gp activity must be considered when administering the new oral anticoagulants. Bleeding concerns remain and must be also addressed when treating with these new agents.

Nursing Implications Prevention of VTE is considered a major component of patient care management in

![Table 5. Comparison of Dabigatran, Rivaroxaban, and Apixaban Properties](image)
The recognition of VTE is difficult and costly and can present a clinical challenge. Symptoms of VTE many times are unspecific and often are asymptomatic (Geerts et al., 2008). Because of this, nursing needs to understand and promote the use of well-designed tools and guidelines for VTE presence and risk assessment (Welle, 2011), as it is often the nurse who initially recognizes the presence or risk for VTE. It is important for the nurse to conduct a thorough history and physical assessment, monitor response to treatment, and interpret assays and vital signs to ensure a comprehensive assessment of VTE presence and risk.

Rivaroxaban is the first new oral anticoagulant that orthopedic nurses are currently administrating to their patients. To facilitate and ensure effective patient teaching and safe administration regarding any VTE prophylactic treatment, the nurse must understand the properties of each modality, specific target effect on the coagulation cascade, potential complications, drug–drug or drug–food interactions, and necessary monitoring. In order for patients to fully embrace and understand their VTE treatment regimen, it is essential that nurses ensure that patients are partners in the educational process (Morrison, 2006).

To enhance prevention of VTE, it is also important for nurses to promote collaboration and effective communication among the care team, to understand and embrace new anticoagulant agents and VTE modalities, to participate in the writing of VTE guidelines or risk assessment algorithms, and to actively conduct or participate in research to ensure the best practice (FitzPatrick, Reilly, & Stavroupoulos, 2006; Welle, 2011). One of the ways in which nursing could enhance understanding of why physicians choose one method of VTE prophylaxis over another is simply to ask. It is important for orthopedic nurses to familiarize themselves with a summary of the AACP and AAOS guideline recommendations. As stated earlier in this article, bleeding risk is highly regarded by orthopedic surgeons when choosing a VTE prophylactic modality. Nurses need to be aware of why and how to measure bleeding risks. In addition to the nurse–physician communication, it is important to maintain open channels with pharmacists as they can provide a wealth of information regarding the new oral anticoagulants.

The Institute of Medicine (2010) charges that the professional formation of every nurse must include new competencies in decision making, quality improvement, systems thinking, and team leadership. To achieve optimal outcomes, the Institute of Medicine states that nurses must become full partners with physicians and the healthcare team in redesigning healthcare through open communication, systems analysis, goal establishment, and participating and serving in leadership roles in decision-making policies.

Because new drug research is rapidly advancing, it is important to research and understand new technology and agents to properly assess, monitor, evaluate, and educate. As in the case of the new oral anticoagulants, the embrace of rapidly emerging new treatments will be both challenging and exciting for nurses.

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