Newer Oral Anticoagulants

Since 2010, the U.S. Food and Drug Administration (FDA) has approved two new oral anticoagulants with unique mechanisms of action. These drugs present alternatives to oral warfarin.

Dabigatran (Pradaxa®) is a direct thrombin inhibitor approved only for use in patients with nonvalvular atrial fibrillation (AF).

Rivaroxaban (Xarelto®) is a direct factor Xa inhibitor with 2 indications:

- For prophylaxis of deep venous thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery
- To reduce the risk of stroke and systemic embolism in patients with nonvalvular AF

A third oral anticoagulant, apixaban (Eliquis®) is also a direct factor Xa inhibitor, but is not yet FDA-approved for any indication.

Before development of the new oral anticoagulants, warfarin was the only oral anticoagulant available. Its FDA-approved uses are:

1. Prophylaxis and treatment of venous thrombosis and PE
2. Prophylaxis and treatment of thromboembolic complications associated with AF and/or heart valve replacement
3. Reduction in the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization after myocardial infarction

Warfarin is a vitamin K antagonist. Its safe use requires avoidance of many interacting foods and drugs and frequent international normalized ratio (INR) testing to guide dose adjustments. In contrast, because of predictable pharmacokinetic effects at FDA-approved doses, the new oral anticoagulants do not require routine laboratory monitoring and can be administered at fixed doses. They also have few food and drug interactions. In case of overdose or pathologic
bleeding, warfarin may be reversed with the administration of oral or parental vitamin K₁. There are no specific reversal agents (antidotes) for the new oral anticoagulants.

Description of Disease.

Stroke and Systemic Embolism in Patients with AF

AF is one of the most common cardiac arrhythmias, affecting 2.66 million Americans. The Centers for Disease Control (CDC) estimates that by the year 2050, 12 million people will have AF. (1) The median age of patients with AF is 66.8 years for men and 74.6 years for women. (1) The disease is characterized by uncoordinated atrial activation with consequent loss of atrial mechanical function that may lead to dizziness and weakness, congestive heart failure, ventricular tachycardia, and embolic cerebrovascular accident. (2) Despite major advances in its management, AF remains a significant cause of cardiovascular morbidity and mortality, primarily due to the increased risk of ischemic stroke and heart failure. Patients with AF are 5 times more likely to have an ischemic stroke than those without AF, and up to 15% of all strokes are attributed to AF. (3) The CHADS₂ risk score is a commonly used tool for the estimation of stroke risk in patients with AF. (4) Five major risk factors for stroke are included, as shown in Table 1. The estimated annual stroke risk correlated with each risk score is listed in Table 2.

Table 1. CHADS₂ Risk Factors for Stroke in AF Patients (4)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥75 years</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Prior stroke or TIA</td>
<td>2</td>
</tr>
<tr>
<td>Total CHADS₂ score</td>
<td></td>
</tr>
<tr>
<td>TIA, transient ischemic attack</td>
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</tbody>
</table>

Table 2. Estimated Annual Stroke Risk Based on CHADS₂ Risk Score(4)

<table>
<thead>
<tr>
<th>Total CHADS₂ Score</th>
<th>Annual Stroke Risk (%)</th>
</tr>
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<tr>
<td>0</td>
<td>1.9</td>
</tr>
<tr>
<td>1</td>
<td>2.8</td>
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<td>2</td>
<td>4.0</td>
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<td>12.5</td>
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<tr>
<td>6</td>
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</table>

An alternate tool for the assessment of stroke risk is the CHA₂DS₂-VASc risk score. (5) This score is similar to the CHADS₂ score but adds an additional point for age 75 years or more and additional risk categories of vascular disease, age 65 to 74 years, and female sex. The CHA₂DS₂-VASc score has been found to better identify low-risk patients than the CHADS₂ score. (6)
AF is classified by duration: Paroxysmal AF terminates spontaneously within 7 days, persistent AF is present continuously for more than 7 days, and permanent AF persists for more than one year and is refractory to cardioversion. A large majority of AF patients are asymptomatic, and AF in itself may not be life-threatening. Commonly, patients report nonspecific symptoms such as fatigue, dyspnea, dizziness, diaphoresis, and palpitations. Occasionally, patients present with extreme manifestations of hemodynamic compromise, such as chest pain, pulmonary edema, or syncope. AF is present in 10% to 40% of patients with a new ischemic stroke. (7)

The two main goals of AF management are to control rate and rhythm and to prevent stroke. Current evidence-based practice guidelines recommend a risk-stratified approach for the use of aspirin, clopidogrel, and oral anticoagulants for stroke prevention in patients with AF (see Practice Guidelines and Position Statements).

**Venous Thromboembolism in Patients Undergoing Knee or Hip Replacement Surgery**

Following total hip replacement surgery (THR), thromboembolism can occur in vessels in the pelvis, thigh, and calf. Without thromboprophylaxis, the incidence of objectively confirmed, hospital-acquired DVT is approximately 40% to 60% following major orthopedic surgery. (8) Several factors contribute to postoperative thrombus formation and propagation of thrombi (8):

- persistent venous injury
- stasis due to continued reduced mobility
- impairment of the endogenous anticoagulant or fibrinolytic systems
- prolonged impairment of venous function

Symptomatic venous thromboembolism (DVT or PE) most commonly presents after orthopedic patients are discharged from the hospital. This may result from extension of an asymptomatic DVT as thromboprophylaxis is discontinued or formation of a new thrombosis during recovery in a rehabilitation center or at home. (8) Most DVTs are clinically silent and resolve spontaneously without any long-term sequelae. Symptoms may develop as a result of venous occlusion or embolization to the lungs (8) and include (9):

- pain and tenderness in the calf and thigh
- positive Homan's sign (pain in the calf or popliteal region elicited with abrupt flexion of the patient's ankle by the examiner while the knee is flexed to 90 degrees)
- unilateral swelling and erythema of the leg
- low-grade fever
- rapid pulse

Prevention of fatal PE is the most important goal of thromboprophylaxis. (10) Proximal thrombi in the popliteal vein and above have been thought to pose a greater risk of PE than calf vein thrombi. (11) Although the risk of DVT without thromboprophylaxis is greater after total knee replacement surgery (TKR) than after THR, (8) proximal DVT occurs less commonly after TKR. Most PEs are asymptomatic. Symptomatic PE can present with pleuritic chest pain, diaphoresis, shortness of breath, and cough. (9) In a group of 30,714 patients undergoing elective THR at the Mayo Clinic, the 30-day mortality rate from PE was 0.04%. (9) Following TKR, the risk of
asymptomatic PE may be as high as 20%, with symptomatic PE reported in 0.5% to 3% of patients and a mortality rate of 2%. (11)

Venography (x-ray of the veins after injection of radiopaque dye) is considered the most sensitive and specific test for the detection of calf and thigh thrombi, but it does not reliably detect pelvic vein thrombi. In addition to being costly, uncomfortable, and invasive, venography carries the risk of anaphylactic reaction to the contrast media and a small risk of inducing DVT. (9, 11) Drugs currently used for DVT/PE prophylaxis in patients undergoing TKR or THR include the low molecular-weight heparins (LMWH), enoxaparin (Lovenox®) and dalteparin (Fragmin®), the synthetic pentasaccharide, fondaparinux (Arixtra®), unfractionated heparin, and warfarin. Each of these is administered subcutaneously except for warfarin, which is oral.

**Acute Venous Thromboembolism**

Venous thromboembolism (VTE) can occur in any vein but most commonly occurs in the leg veins. The major complication of thrombosis of the deep veins of the legs (DVT) is pulmonary embolism (PE). Post-phlebitic syndrome due to damage of venous valves also can occur. DVT of the large proximal veins (popliteal, femoral, or iliac) leads to PE or post-phlebitic syndrome more commonly than small thrombi of the distal calf veins. (12)

VTE occurs in both hospitalized patients and in otherwise healthy outpatients. VTE is caused by the triad of stasis (e.g., immobility, increased venous pressure), vascular injury, and hypercoagulability (Virchow’s triad). Patients with a past history of VTE have an increased risk of future VTE. Symptoms and signs of VTE result from obstruction to venous outflow, inflammation of the vessel wall, or embolization of thrombus into the pulmonary circulation. However, most thrombi are asymptomatic. Asymptomatic PE is detected by perfusion lung scanning in approximately 50% of patients with documented proximal vein thrombosis, and asymptomatic VTE. Conversely proximal DVT is found in approximately 70% of patients with confirmed PE. Proximal vein thrombosis has a recurrence rate over 3 months of 47% if inadequately treated but 2% to 4% when treated with oral anticoagulants or subcutaneous heparin. After 3 months of anticoagulant therapy, the recurrence rate is 5% to 10% during the following year. (12)

**Acute Coronary Syndromes**

Acute coronary syndromes (ACS) are caused by acute myocardial ischemia, i.e., lack of oxygen to cardiac muscle cells. ACS includes 3 clinical presentations: unstable angina, non-ST segment elevation myocardial infarction (NSTEMI), and ST segment elevation myocardial infarction (STEMI). In the U.S., approximately 900,000 individuals suffer an MI annually, 20% of whom die before reaching the hospital, and 30% die within 30 days. (13)

Unstable angina is defined as angina (chest pain or pressure) occurring at rest or with minimal exertion, new-onset angina, or worsening symptoms in a previously stable patient, such as increased frequency or duration of attacks, resistance to previously effective medications, or provocation with decreasing levels of exertion.

A universal definition of MI was published by the European Society of Cardiology in 2012. (6) Acute MI describes myocardial necrosis in a clinical setting suggesting acute myocardial ischemia. Additional criteria for making the diagnosis include: a typical rise and fall of a serum cardiac biochemical marker (either troponin or the muscle-brain fraction of creatine kinase [CK-MB]), clinical symptoms, electrocardiogram (EKG) changes, imaging or angiographic findings,
and coronary artery intervention (i.e., percutaneous coronary intervention [PCI] or coronary artery bypass graft surgery [CABG]).

Acute MI is classified at presentation by findings on the EKG, as either STEMI or NSTEMI. Depression or no change of the ST segment is associated with subendocardial ischemia, affecting the inner layers of the ventricular wall. ST elevation suggests transmural injury. The differentiation between STEMI and NSTEMI has important implications in terms of management, therapeutic intervention, outcome, and prognosis. (13)

The twin goals of treatment of ACS are the immediate relief of ischemia and the prevention of serious adverse outcomes (i.e., death, MI, or re-infarction). Treatments include anti-ischemic therapy (e.g., oxygen, nitroglycerin, and beta-blockers), antithrombotic therapy, and reperfusion.

Regulatory Status

- Rivaroxaban received FDA approval for prophylaxis of DVT and PE in patients undergoing knee or hip replacement surgery in July 2011, and for prevention of stroke and systemic embolism in patients with nonvalvular AF in November 2011. In June 2012, a new drug application (NDA) for rivaroxaban in secondary prevention of acute coronary syndromes (ACS) received a Complete Response Letter from the FDA. An FDA Advisory Committee cited concerns about missing data in the pivotal ATLAS-ACS 2 TIMI 51 trial (14) and increased bleeding risk with rivaroxaban. (15)

- Rivaroxaban received an additional FDA approval in November 2012 for acute treatment of DVT and/or PE and long-term prophylaxis of thromboembolism.

- Dabigatran received FDA approval to reduce the risk of stroke and systemic embolism in patients with nonvalvular AF in October 2010. Dabigatran is not approved in the U.S. for thromboprophylaxis after TKR and THR but is approved for this indication in Europe and Canada. The manufacturer of dabigatran (Boehringer-Ingelheim) has not filed an NDA for this indication to the FDA after dabigatran failed to demonstrate noninferiority to the FDA-approved dose of enoxaparin in the RE-MOBILIZE TKR trial. (11) The FDA-approved dose of enoxaparin for this indication is 30 mg subcutaneously twice daily starting on the morning after surgery. The dose approved in Europe is 40 mg subcutaneously once daily starting the evening before surgery.

- Apixaban currently is not FDA-approved for any indication. In June 2012, an NDA for apixaban for stroke prevention in patients with nonvalvular AF received a Complete Response Letter from the FDA requesting additional information about a pivotal trial. Apixaban is approved in Europe for thromboprophylaxis after THR and TKR.

Policy

Rivaroxaban (Xarelto®) and dabigatran (Pradaxa®) may be considered medically necessary in adult patients 18 years of age or older with documented paroxysmal, persistent, or permanent atrial fibrillation (AF) not complicated by valvular disease, as an alternative to warfarin therapy.

Rivaroxaban (Xarelto®) and dabigatran (Pradaxa®) may be considered medically necessary for prophylaxis of deep vein thrombosis and pulmonary embolism in adult patients 18 years of age or older who are undergoing knee or hip replacement surgery.
Rivaroxaban (Xarelto®) may be considered **medically necessary** for treatment of acute DVT or PE, including long-term treatment and secondary prevention of thromboembolism.

Dabigatran (Pradaxa®) is considered **investigational** for treatment of acute DVT or PE, including long-term treatment and secondary prevention of thromboembolism.

The use of dabigatran and rivaroxaban is considered **investigational** for all other indications, including but not limited to:

1. Prophylaxis of DVT and PE in hospitalized medically ill patients
2. Secondary prevention of cardiovascular events after an acute coronary syndrome
3. To reduce the risk of stent thrombosis in patients with acute coronary syndromes

The use of apixaban (Eliquis®) is considered **investigational** for all uses.

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**Policy Guidelines**

Active pathological bleeding is a contraindication to dabigatran and rivaroxaban.

Dose adjustment is required in patients with reduced creatinine clearance (CrCl):

**Dabigatran**

- For patients with CrCl >30 mL/min: 150 mg orally, twice daily
- For patients with CrCl 15-30 mL/min: 75 mg orally, twice daily
- Patients with CrCl ≤30 mL/min were excluded from the pivotal trial for dabigatran.

**Rivaroxaban**

- For patients with CrCl >50 mL/min: 20 mg orally, once daily with the evening meal
- For patients with CrCl 15 - 50 mL/min: 15 mg orally, once daily with the evening meal
- Patients with CrCl <30 mL/min were excluded from the pivotal trial for rivaroxaban.

Use of both drugs in patients with renal failure should be avoided. The cutoff for the definition of renal failure is not standardized; some recommendations have used a CrCl <15 mL/min and others have used a CrCl<30.

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**Rationale**

This policy was created in September 2012 based on TEC Specialty Pharmacy Reports #14-2010 “Dabigatran/Pradaixa®” (16) and #15-2011 “Rivaroxaban/Xarelto®”. (17) This policy will review randomized controlled trials (RCTs) in 4 disease categories that have used one of the newer oral anticoagulant medications and have evaluated at least one of the following clinical outcomes:

- Prevention of stroke and systemic embolism in patients with atrial fibrillation (AF)
- Prophylaxis of venous thromboembolism in patients undergoing knee or hip replacement surgery
- Treatment of acute deep venous thrombosis (DVT) and/or pulmonary embolism (PE)
Secondary prevention in acute coronary syndromes (ACS)

**LITERATURE REVIEW**

**Prevention of Stroke and Systemic Embolism in Patients with AF**

*Rivaroxaban.*

**Rocket AF trial.** The efficacy of rivaroxaban to reduce the risk of stroke and systemic embolism in patients with nonvalvular AF was assessed in the pivotal “Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonist for Prevention of Stroke and Embolism Trial in Atrial Fibrillation” (ROCKET AF; N=14,264). (18) ROCKET AF was a 4-year, randomized, controlled, double-blind, double-dummy, noninferiority trial. Enrolled patients were adults with nonvalvular AF who were at moderate to high risk of future stroke or systemic embolism, as evidenced by a history of prior stroke, transient ischemic attack (TIA), or systemic embolism, or by a CHADS2 risk score of 2 or more. Patients scheduled for electrical or pharmacological cardioversion and those with creatinine clearance (CrCl)<30 mL/min were excluded. Patients were randomized to receive rivaroxaban 20 mg orally daily (15 mg in those with CrCl 30-49 mL/min) or dose-adjusted warfarin. The primary efficacy endpoint was the incidence of stroke or systemic embolism. Median patient age was 73 years, and mean CHADS2 score was 3.5. Patients randomized to warfarin were in the therapeutic range 55% of the time.

In the per protocol population, rivaroxaban was not inferior to warfarin based on a noninferiority margin of 1.38. Primary endpoint event rates per 100 patient-years were 1.7 in rivaroxaban–treated patients and 2.2 in warfarin–treated patients (hazard ratio [HR]: 0.79 [95% confidence interval (CI): 0.66, 0.96], p<0.001). Subsequent prespecified testing failed to demonstrate superiority. In the intent-to-treat population, rivaroxaban was inferior to warfarin. Primary efficacy endpoint event rates per 100 patient-years were 2.1 in rivaroxaban–treated patients and 2.4 in warfarin–treated patients (HR: 0.88 [95% CI: 0.75, 1.03], p=0.117). Rates per 100 patient-years of myocardial infarction (MI) (0.9 rivaroxaban vs. 1.1 warfarin, HR: 0.81 [95% CI: 0.63, 1.06], p=0.121) and all-cause mortality (1.9 rivaroxaban vs. 2.2 warfarin, HR: 0.85 [95% CI: 0.70, 1.02], p=0.073) did not differ statistically between treatment groups.

The primary safety outcome in ROCKET AF was the composite of major bleeding (defined as fatal bleeding, bleeding in a critical area or organ, bleeding leading to permanent disability, a decrease in hemoglobin of at least 2 g/dL, or transfusion of at least 2 units of blood) and non-major clinically relevant bleeding (defined as overt bleeding associated with medical intervention, temporary interruption of study drug, or patient discomfort). The event rate per 100 person-years for this outcome was 14.9 in rivaroxaban–treated patients and 14.5 in warfarin–treated patients (HR: 1.03, 95% CI: 0.96, 1.11, p=0.442). Compared to warfarin–treated patients, rivaroxaban–treated patients had:

- Fewer intracranial hemorrhages (0.5 vs. 0.7 per 100 patient-years, HR: 0.67, 95% CI: 0.47, 0.93; p=0.019)
- Fewer critical organ bleeds (0.8 vs. 1.2 per 100 patient-years, HR: 0.69, 95% CI: 0.53, 0.91; p=0.007)
- Fewer bleeding-related deaths (0.2 vs. 0.5 per 100 patient-years, HR: 0.50, 95% CI: 0.31, 0.79; p=0.003)
Dabigatran.

RE-LY trial. (19) Evidence for the efficacy of dabigatran for the prevention of stroke and systemic embolism in patients with nonvalvular AF comes from the international Phase III “Randomized Evaluation of Long Term Anticoagulant Therapy” (RE-LY) trial. RE-LY was a 3-year trial that enrolled 18,113 patients with nonvalvular AF and at least one risk factor for stroke. Patients with CrCl <30 mL/min were excluded. Thirty-six percent of patients were recruited from North America. A prospective, randomized, open-label, blinded-endpoint (PROBE) trial design was used. There were 3 treatment arms: 1) dabigatran 110 mg twice daily; 2) dabigatran 150 mg twice daily; 3) dose-adjusted warfarin with target international normalized ratio (INR) of 2.0 to 3.0. The primary efficacy endpoint was the incidence of stroke or systemic embolism. Secondary endpoints included the incidence of hemorrhagic stroke and MI. The primary objective of the trial was to test each dose of dabigatran for noninferiority to dose-adjusted warfarin for the primary efficacy outcome. Mean patient age was 71.5, and mean CHADS2 score was 2.1. For patients randomized to warfarin, mean proportion of time in the therapeutic range was 64%.

For the primary efficacy endpoint, both doses of dabigatran were noninferior to warfarin based on a noninferiority margin of 1.46. Only the 150-mg dose was superior to warfarin (relative risk [RR]: 0.65 [95% CI: 0.52, 0.81], p<0.001; ARR=1.1 percentage points, number needed to treat [NNT]=87). Both doses of dabigatran significantly decreased the risk of hemorrhagic stroke compared to warfarin (150 mg dabigatran: RR: 0.26 [95% CI: 0.14, 0.49], p<0.001; ARR=0.6 percentage points, NNT=182; 110 mg dabigatran: RR: 0.31 [95% CI: 0.17, 0.56], p<0.001; ARR=0.5 percentage points, NNT=194). Both doses of dabigatran were associated with statistically nonsignificant increases in the risk of MI (150 mg dabigatran: RR: 1.27 [95% CI: 0.94, 1.71], p=0.12; 110 mg dabigatran: RR: 1.29 [95% CI: 0.96, 1.75], p=0.09).

The primary safety endpoint was major bleeding, which was defined as life-threatening or fatal bleeding, a decrease in hemoglobin of at least 2 g/dL, transfusion of at least 2 units of blood, or symptomatic bleeding in a critical area or organ. Although there was no significant difference in the risk of major bleeding with 150 mg of dabigatran relative to warfarin (RR: 0.93, p=0.32), 110 mg of dabigatran was associated with a 20% reduction in the risk of major bleeding relative to warfarin (p=0.003, ARR=1.3%, NNH=77). Patients in the higher dose dabigatran group had a 48% greater risk of major gastrointestinal bleeding compared to patients taking warfarin (p<0.001, AR=1.0%, NNH=100). The risk of major gastrointestinal bleeding in the lower dose dabigatran group was not statistically different from that in the warfarin group (p=0.52).

In the RE-LY trial, elevations in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than 3 times the upper limit of normal (ULN) concurrent with bilirubin elevations greater than 2 times ULN occurred in 0.2% of patients in both dabigatran groups and in 0.3% of patients in the warfarin group.

Apixaban.
The efficacy of apixaban for prevention of stroke and systemic embolism was studied in two international, active-controlled, double-blind RCTs.

**AVERROES trial** (20) The “Apixaban vs. Acetylsalicylic Acid to Prevent Strokes” (AVERROES) trial compared apixaban to aspirin in 5,599 patients with nonvalvular AF and at least one additional risk factor for stroke. Patients were demonstrated or expected to be unsuitable candidates for adjusted-dose vitamin K antagonist (VKA) therapy. (Forty percent of patients had previously received but discontinued VKA, most because INR could not be maintained in a therapeutic range. Other reasons for unsuitability for VKA therapy included inability to obtain or physician assessment of being unlikely to obtain INR measurements at requested intervals in 43% of patients; VKA therapy considered inappropriate in 21% of patients with a CHADS2 score of 1; and 37% of patients did not want to take VKA.) Patients with CrCl less than 25 mL/min were excluded. For 94% of patients, apixaban was dosed at 5 mg orally twice daily; patients who met 2 or more of the following criteria (6%) received 2.5 mg twice daily: age ≥80 years, weight ≤60 kg, or serum creatinine ≥1.5 mg/dL. Aspirin was dosed at investigator discretion; 64% of patients received 81 mg daily, 27%, 162 mg daily, 2%, 243 mg daily, and 7%, 324 mg daily. The primary efficacy outcome was the incidence of stroke or systemic embolism. The mean age of all patients was 70 years, and mean CHADS2 score was 2.0±1.1. Fourteen percent of patients had had a prior stroke. The trial was terminated early due to benefit of apixaban. During a mean follow-up of 1.1 years, the observed rate of stroke or systemic embolism was 1.6% per year in the apixaban group and 3.7% per year in the aspirin group (HR: 0.45 [95% CI: 0.32, 0.62]; NNT=45).

The primary safety outcome was the incidence of major bleeding, defined as clinically overt bleeding accompanied by one or more of the following: a decrease in the hemoglobin level of at least 2 g/dL over a 24-hour period, transfusion of 2 or more units of packed red cells, bleeding at a critical site (intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, or retroperitoneal), or fatal bleeding. The rate of major bleeding was 1.4% per year in the apixaban group and 1.2% per year in the aspirin group (HR: 1.13 [95% CI: 0.74, 1.75], p=0.57). The rate of intracranial bleeding was 0.4% per year in both groups. Rates of all-cause mortality were 3.5% per year in the apixaban group and 4.4% per year in the aspirin group (HR: 0.79 [95% CI: 0.62, 1.02], p=0.07).

**ARISTOTLE trial** (21) The “Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation” (ARISTOTLE) trial was an international, double-blind, double-dummy, noninferiority RCT that compared apixaban to dose-adjusted warfarin (target INR: 2.0 to 3.0). Patients (N=18, 201) had nonvalvular AF or atrial flutter and at least one additional risk factor for stroke. Patients with CrCl <25 mL/min were excluded. For 95% of patients, apixaban was dosed at 5 mg orally twice daily; the remaining 5% of patients met 2 or more of the criteria identified above for the AVERROES trial and received 2.5 mg twice daily. The primary efficacy outcome was the incidence of stroke or systemic embolism with a noninferiority margin of 1.44. Median patient age was 70 years, and mean CHADS2 score was 2.1±1.1. For patients randomized to warfarin, the mean proportion of time in the therapeutic range was 62%.

During a median follow-up of 1.8 years, the rate of the primary efficacy outcome was 1.27% per year in the apixaban group and 1.60% per year in the warfarin group (HR: 0.79 [95% CI: 0.66, 0.95]). Superiority was tested in a pre-specified hierarchical testing procedure and also was statistically significant (p<0.001). The reduction in the hazard for hemorrhagic stroke (HR: 0.51 [95% CI: 0.35, 0.75]) was greater than that for ischemic or indeterminate stroke (HR: 0.92 [95%
CI: 0.74, 1.13]). All-cause mortality was lower with apixaban compared with warfarin (HR: 0.89 [95% CI: 0.80, 0.998], p=0.047).

Apixaban reduced the risk of major bleeding by 31% compared to warfarin (HR: 0.69 [95% CI: 0.60, 0.80]). There was no evidence of a difference in major gastrointestinal (GI) bleeding between apixaban and warfarin (HR: 0.89 [95% CI: 0.70, 1.15]).

Conclusions.

For stroke prevention in atrial fibrillation, all 3 oral anticoagulant agents, dabigatran, rivaroxaban, and apixaban, have demonstrated non-inferiority to warfarin in large, RCTs. In addition, superiority over warfarin for decreasing stroke and systemic emboli was reported for apixaban and for 1 of 2 doses of dabigatran. Rates of bleeding have been mixed, with most studies reporting similar or lower overall rates of bleeding and lower rates of intracranial hemorrhage compared to warfarin. Recent guidelines on stroke prevention in atrial fibrillation have favored a newer oral anticoagulant over warfarin, with caveats about the lack of long-term evidence, and other concerns such as the lack of an effective antidote.

Table 3. RCTs of Newer Anticoagulant Agents Versus Warfarin (or Aspirin) for Prevention of Stroke and Systemic Embolism in Patients with Atrial Fibrillation

<table>
<thead>
<tr>
<th>Study/Year</th>
<th>FU Group</th>
<th>N</th>
<th>Composite outcome (%/yr)</th>
<th>Ischemic Stroke (%/yr)</th>
<th>Hemorrhagic Stroke (%/yr)</th>
<th>Overall Mortality (%/yr)</th>
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<td>Warfarin (dose-adjusted)</td>
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<td>Conolly 2009</td>
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<td>1.34e</td>
<td>0.12</td>
<td>3.75</td>
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<td>1.71d</td>
<td>1.21e</td>
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<td>[RE-LY]</td>
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<td>Warfarin</td>
<td>60221.71d</td>
<td>1.24e</td>
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Apixaban

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<td>[ARISTOTLE]</td>
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<td></td>
<td>0.92, p=0.01</td>
<td>0.51, p&lt;0.001</td>
<td>0.89, p=0.047</td>
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<td>Conolly 2011</td>
<td>Apixaban 5 mg BID</td>
<td>2808</td>
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Prophylaxis of Venous Thromboembolism in Patients Undergoing Knee or Hip Replacement Surgery

Rivaroxaban. RECORD trials. The development program of rivaroxaban for thromboprophylaxis in total knee replacement therapy (TKR) and total hip replacement surgery (THR) included 4 international, randomized, active-controlled, double-blind, double-dummy trials. These are the “Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism” (RECORD) trials, which compared oral rivaroxaban to subcutaneous enoxaparin. RECORD 1 (22) and 2 (23) were conducted in patients undergoing elective THR, and RECORD 3 (24) and 4 (25) were conducted in patients undergoing elective TKR. RECORD 1 and 4 were designed as noninferiority trials. In both trials, noninferiority of rivaroxaban to enoxaparin was shown, and superiority was tested. RECORD 4 was not considered in the U.S. Food and Drug Administration’s (FDA) approval decision due to numerous trial conduct violations.

In all 4 RECORD trials, rivaroxaban 10 mg was administered once daily beginning 6 to 8 hours after surgery. In 3 of the RECORD trials, enoxaparin 40 mg was administered once daily starting 12 hours preoperatively. This is not the FDA-approved dose of enoxaparin for TKR. One of the 2 TKR trials administered enoxaparin at the FDA-approved dose of 30 mg twice daily starting 12 to 24 hours postoperatively. Treatment duration was 14 days in the TKR trials and 35 days in one of the THR trials. In the other THR trial (RECORD 2), rivaroxaban was administered for 35 days and enoxaparin was administered for 12 days. The primary efficacy outcome was incidence of total venous thromboembolism (VTE), a composite of:

- Any deep venous thrombosis (DVT, proximal or distal; symptomatic or venographic),
- Nonfatal pulmonary embolism, and
- Death from any cause.
A total of 12,729 patients were randomized in the 4 trials. Thirty to forty percent of randomized patients were excluded from the primary efficacy analysis primarily due to inadequate assessment of DVT. Sensitivity analyses were performed using all randomized patients and various scenarios for patients with missing responses. These analyses support the following efficacy findings.

**For patients undergoing THR:**

- In RECORD 1, the incidence of total VTE was 1.1% in the rivaroxaban group and 3.7% in the enoxaparin group, with a treatment duration of 35 days for both drugs (p<0.001, number needed to treat [NNT]=39).
- In RECORD 2, the incidence of total VTE was 2.0% in the group receiving rivaroxaban for 35 days and 9.3% in the group receiving enoxaparin for 12 days (p<0.001, NNT=14).

**For patients undergoing TKR:**

- In RECORD 3, the incidence of total VTE was 9.6% in the rivaroxaban group and 18.9% in the group receiving enoxaparin 40 mg once daily, an FDA-unapproved dose (p<0.001, NNT=11).
- In RECORD 4, the incidence of total VTE was 6.9% in the rivaroxaban group and 10.1% in the group receiving enoxaparin 30 mg twice daily (p=0.012, NNT=32). Because of numerous conduct, oversight, and data collection issues, FDA considered results from this trial unreliable and excluded them from deliberations for approval. (26)

Major bleeding was the primary safety outcome in the RECORD trials. The incidence of major bleeding was 0.39% in the rivaroxaban group and 0.21% in the enoxaparin group (p=0.08). The incidence of major plus clinically relevant non-major bleeding (including surgical site bleeding) was 3.19% in the rivaroxaban group and 2.55% in the enoxaparin group, p=0.04. One death from gastrointestinal hemorrhage occurred in a rivaroxaban–treated patient who also was taking nonsteroidal anti-inflammatory drugs.

The incidence of cardiovascular events during the on-treatment phase of the RECORD trials was similar between treatment groups. At 30 to 35 days after the last dose of study drug, 5 ischemic strokes (0.08%) occurred among rivaroxaban–treated patients and 1 ischemic stroke (0.02%) occurred among enoxaparin–treated patients. The occurrence of alanine aminotransferase (ALT) greater than 3 times the upper limit of normal (ULN) concurrent with total bilirubin greater than 2 times ULN occurred in 9 (0.15%) rivaroxaban-treated patients compared to 7 enoxaparin–treated patients (0.11%).

*Dabigatran.* Four RCTs compared dabigatran to enoxaparin for thromboprophylaxis following TKR (REMOBILIZE (27) and REMODEL (28)) or THR (RENOVATE (29) and RENOVATE II (30)) in 10,265 patients. All 4 were randomized, double-blind, noninferiority trials in adult patients (≥18 years of age) undergoing elective unilateral procedures. Both TKR trials and one THR trial (RENOVATE) evaluated dabigatran doses of 220 mg and 150 mg orally daily. The other THR trial (RENOVATE II) assessed only the 220 mg dose of dabigatran. In all trials, dabigatran was initiated within 1 to 12 hours postoperatively at half the dose for the first dose. Only one TKR trial (REMOBILIZE) used FDA-approved dosing of enoxaparin (30 mg subcutaneously twice daily initiated 12 hours postoperatively). The other TKR trial (REMODEL) used European dosing, i.e., 40 mg once daily initiated the evening before surgery. Treatment duration continued for 6 to 13 days in the TKR trials and for 28 to 35 days in the THR trials.
all trials, the primary efficacy outcome was a composite of symptomatic or venographic DVT, symptomatic PE, and all-cause mortality during treatment.

As in the RECORD trials, the primary efficacy analyses excluded 25% to 30% of patients, primarily due to inadequate or missing venography.

For patients undergoing THR, efficacy findings were:

- In RENOVATE, the incidence of total VTE and all-cause mortality was 6.0% in the dabigatran 220 mg group (absolute difference from placebo -0.7% [95% CI: -2.9, 1.6], p<0.001), 8.6% in the dabigatran 150 mg group (absolute difference from placebo 1.9% [95% CI: -0.6, 4.4], p<0.001), and 6.7% in the enoxaparin group. Both doses of dabigatran were noninferior to enoxaparin at a noninferiority margin of 7.7% difference in incidence.

- In RENOVATE II, the incidence of total VTE and all-cause mortality was 7.7% in the dabigatran 220 mg group and 8.8% in the enoxaparin group (absolute difference -1.1% [95% CI: -3.8, 1.6], p<0.001). Dabigatran was non-inferior to enoxaparin at a noninferiority margin of 7.7% difference in incidence.

For patients undergoing TKR, efficacy findings were:

- In REMODEL, the incidence of total VTE and all-cause mortality was 36.4% in the dabigatran 220 mg group (absolute difference from placebo -1.3% [95% CI: -7.3, 4.6], p<0.001), 40.5% in the dabigatran 150 mg group (absolute difference from placebo 2.8% [95% CI: -3.1, 8.7], p=0.02), and 37.7% in the enoxaparin 40 mg once daily group. Both doses of dabigatran were noninferior to enoxaparin at a noninferiority margin of 9.2% difference in incidence.

- In REMOBILIZE, the incidence of total VTE and all-cause mortality was 31.1% in the dabigatran 220 mg group (absolute difference from placebo 5.8% [95% CI: 0.8, 10.8], p=0.02), 33.7% in the dabigatran 150 mg group (absolute difference from placebo 8.4% [3.4, 13.3], p=0.001), and 25.3% in the enoxaparin 30 mg twice daily group. Both doses of dabigatran were inferior to enoxaparin at a noninferiority margin of 9.2% difference in incidence.

The primary safety outcome in the TKR and THR trials was the incidence of major bleeding events during study treatment. No statistical difference in this outcome was observed between treatment groups. In the THR trials, incidence of on-treatment major bleeding was 2.0% and 1.4% for the dabigatran 220 mg groups, 1.3% for the dabigatran 150 mg group (RENOVATE only), and 1.6% and 0.9% for the enoxaparin groups in RENOVATE and RENOVATE II, respectively. In the TKR trials, incidence of on-treatment major bleeding was 1.5% and 0.6% for the dabigatran 220 mg groups, 1.3% and 0.6% for the dabigatran 150 mg groups, and 1.3% (40 mg daily) and 1.4% (30 mg twice daily) for the enoxaparin groups in REMODEL and REMOBILIZE respectively.

Two sponsor-funded meta-analyses of the RENOVATE, REMODEL, and REMOBILIZE trials have been published; the RENOVATE-II trial in THR had not been published at the time of either meta-analysis. Both analyses reported pooled results for the primary efficacy outcome (total VTE and all-cause mortality) and for the primary safety outcome (major bleeding). Wolowacz et al. (31) reported risk ratios for the 220 mg dose of dabigatran compared to enoxaparin using random effects models, which are considered more conservative than fixed
effects models. Pooled results of the 2 trials that used European enoxaparin dosing (REMODEL in TKR and RENOVATE in THR) supported results of the individual trials. For the primary efficacy endpoint, the risk ratio was 0.95 (95% CI: 0.82, 1.10), I²=0%, and for the primary safety endpoint, 1.24 (95% CI: 0.75, 2.05), I²=0%. The authors did not assume homogeneity of the 2 trials based on the I² statistic because of inherent differences in the trial designs (e.g., different procedures). Analyses of all three trials were consistent with the results of RENOVATE AND REMODEL (risk ratio for efficacy 1.05 [95% CI: 0.87, 1.26], I²=57.7%; risk ratio for safety 0.94 [0.51, 1.75], I²=40.9%). Because the I² statistic indicated moderate to substantial statistical heterogeneity, the authors questioned the appropriateness of pooling trials that used different enoxaparin regimens.

Friedman et al. (32) compared both doses of dabigatran to enoxaparin using risk differences and fixed effects models. Their findings also supported those of the individual trials. For efficacy, pooled risk differences from REMODEL and RENOVATE were -0.9 (95% CI: -2.2, 0.4), I²=0% for the 220 mg dose and 0.3 (95% CI: -1.1, 1.8), I²=0% for the 150 mg dose. For safety, risk differences were 0.3 (95% CI: -0.5, 1.1), I²=0% for the 220 mg dose and -0.2 (95% CI: -0.9, 0.6), I²=0% for the 150 mg dose. Pooling all 3 trials yielded risk differences for efficacy of -0.2 (95% CI: -1.3, 0.9), I²=37% for the 220 mg dose and 0.5 (95% CI: -0.6, 1.6), I²=0% for the 150 mg dose. For safety, risk differences were -0.2 (95% CI: -0.8, 0.5), I²=40% for the 220 mg dose and -0.4 (95% CI: -1.0, 0.2), I²=0% for the 150 mg dose.

In response to post-marketing reports of bleeding events in patients taking dabigatran, FDA modified the product label to provide:

- guidance for assessment of renal function before and during treatment with dabigatran,
- additional information about drug interactions that may increase dabigatran exposure and bleeding risk, and
- clear statements regarding the lack of an antidote for dabigatran.

**Apixaban. ADVANCE trials.** Three Phase III international, randomized, double-blind, active-controlled, noninferiority trials compared oral apixaban to subcutaneous enoxaparin for thromboprophylaxis after elective TKR (ADVANCE-1 (34) and ADVANCE-2 (35)) or THR (ADVANCE-3 (36)). A Phase II trial in patients undergoing TKR (APROPOS (37)) supported the apixaban dose selection. In the phase III trials, patients were randomized to apixaban 2.5 mg twice daily initiated 12 to 24 hours postoperatively or enoxaparin. In trials that used the 40 mg daily enoxaparin dosing schedule (ADVANCE-2 and ADVANCE-3), enoxaparin was started 12 hours before surgery. ADVANCE-1 used the 30 mg twice daily enoxaparin dosing schedule (the FDA-approved dose), initiated 12 hours after surgery. Treatment was given for 10 to 14 days in the TKR trials and for 32 to 38 days in the THR trial. In all trials, the primary efficacy outcome was the on-treatment, adjudicated composite of asymptomatic and symptomatic DVT, nonfatal PE, or death from any cause.

In ADVANCE-1 and ADVANCE-3, 71% of patients had evaluable venograms and were included in the primary efficacy analysis; in ADVANCE-2, 65% of patients were included in the efficacy analysis.

For patients undergoing THR, efficacy findings were:

- In ADVANCE-3, the primary efficacy outcome occurred in 1.4% of patients in the apixaban group and in 3.9% of patients in the enoxaparin group (RR: 0.36 [95% CI:
0.22, 0.54]; p<0.001 for both noninferiority using a margin of 1.25 and superiority; absolute risk reduction [ARR]: 2.5 percentage points [95% CI: 1.5, 3.5], NNT=40 [95% CI: 28, 67]).

For patients undergoing TKR, efficacy findings were:

- In ADVANCE-2, the primary outcome occurred in 15% of patients in the apixaban group and 24% of patients in the enoxaparin 40 mg group (RR: 0.62 [95% CI: 0.51, 0.74]; p<0.001 for both noninferiority using a margin of 1.25 and superiority; ARR: 9.3 percentage points [95% CI: 5.8, 12.7], NNT=11 [95% CI: 8, 18]).

- In ADVANCE-1, the primary outcome occurred in 9.0% of patients in the apixaban group and 8.8% of patients in the enoxaparin group (RR: 1.02 [95% CI: 0.78, 1.32]). As in the REMOBILIZE trial of dabigatran for thromboprophylaxis following TKR described above, apixaban was inferior at a noninferiority margin of 1.25 to the FDA-approved dose of enoxaparin.

The primary safety outcome in the 2 TKR trials (ADVANCE-1 and ADVANCE-2) and in the THR trial (ADVANCE-3) was the composite outcome of major and clinically relevant nonmajor bleeding. In ADVANCE-1 and -2, results for patients undergoing TKR varied:

- In ADVANCE-1, which compared apixaban to enoxaparin at the higher FDA-approved dose, the primary safety outcome occurred in 2.9% of the apixaban group and 4.3% of the enoxaparin group (ARR: -1.5 percentage points [95% CI: -2.8, 0.2], p=0.03). For both groups, drop in hemoglobin level was calculated from the postoperative instead of the preoperative baseline value, which may have underestimated the true major bleeding event rate. (38).

- ADVANCE-2: The primary safety outcome occurred in 53 (3.5%) of 1,501 TKR patients receiving apixaban and 72 (4.8%) of 1,508 treated with enoxaparin (ARR: -1.4 percentage points [95% CI: -2.7, 0.2], p=0.09).

For patients undergoing THR, major and clinically relevant bleeding was similar between groups. In ADVANCE-3, the primary safety outcome occurred in 129 (4.8%) of 2,673 apixaban patients and 134 (5.0%) of 2,659 enoxaparin patients (ARR: -0.2 percentage points [95% CI: -1.4, 1.0], p=0.72).

Conclusions. There are numerous clinical trials for each agent in patients undergoing THR or TKR. For rivaroxaban, the RECORD trials have reported lower rates of thromboembolism compared to LMW heparin. NNTs to prevent one episode of thromboembolism for THR were 14 and 39, and for TKR, 11 and 32. This improvement in efficacy was accompanied by a small increase in major bleeding. Clinical trials of dabigatran (RENOVATE, REMODEL, REMOBILIZE) have generally reported noninferiority to low molecular-weight heparin (LMWH) with a similar rate of major bleeding. The ADVANCE trials have reported that apixaban is either noninferior or superior to LMWH, and the rates of major bleeding have been similar or lower than for LMWH.

Table 4 - Prophylaxis of Venous Thromboembolism in Patients Undergoing Knee or Hip Replacement

<table>
<thead>
<tr>
<th>Study/year</th>
<th>F/UGroup</th>
<th>N</th>
<th>Composite outcome (%/yr)</th>
<th>Ischemic Stroke</th>
<th>Hemorrhagic Stroke</th>
<th>Overall Mortality</th>
<th>Cardiovascular Mortality</th>
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</thead>
</table>

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<thead>
<tr>
<th>Rivaroxaban</th>
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<td>1.16,7</td>
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<td>Enoxaparin 2008</td>
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<td>Kakkar</td>
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<td>Enoxaparin 2008</td>
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<td>&lt;0.1</td>
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<td>Lassen</td>
<td>Rivaroxaban 2008</td>
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<td>Enoxaparin 2008</td>
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<tr>
<td>[RECORD 4]</td>
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<td>p=0.0118</td>
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<p>| Dabigatran |
|-------------|-----------------|-----------------|-----------------|-----------------|
| Ginsberg    | Dabigatran 2009 | 877 33.7a       | --              | 0.2             |
| 2009        | Dabigatran 2009 | 862 31.1a       | --              | 0.2             |
| [REMOBILIZE]| RR, p-value     | --              | --              | --              |
| Eriksson    | Dabigatran 2009 | 708 40.514      | --              | 0.17,14         |
| 2007        | Dabigatran 2009 | 694 36.414      | --              | 0.17,14         |
| [REMODEL]   | Enoxaparin 2009 | 699 37.714      | --              | 0.17,14         |</p>
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<th>NS</th>
<th>RR</th>
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<td>Dabigatran 150 mg/d</td>
<td>1174</td>
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<td>2007</td>
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<td>7.7&lt;sup&gt;15&lt;/sup&gt;, 15</td>
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<td>1019</td>
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**Apixaban**

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment 1</th>
<th>Treatment 2</th>
<th>p value</th>
<th>NS</th>
<th>RR</th>
<th>p value</th>
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<td><strong>Lassen</strong></td>
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<td>1599</td>
<td>9.0&lt;sup&gt;16&lt;/sup&gt;</td>
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<td>Apixaban 2.5 mg BID</td>
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<td>15.1&lt;sup&gt;7,16&lt;/sup&gt;</td>
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<td>2010</td>
<td>Enoxaparin 40 mg /d</td>
<td>1529</td>
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<td><strong>Lassen</strong></td>
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<td>2708</td>
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<td>2010</td>
<td>Enoxaparin 40 mg /d</td>
<td>2699</td>
<td>3.9&lt;sup&gt;7,c&lt;/sup&gt;</td>
<td>--</td>
<td>--</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>[ADVANCE-3]</td>
<td>RR, p value</td>
<td>0.36, p&lt;0.001</td>
<td>--</td>
<td>--</td>
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<td></td>
</tr>
<tr>
<td><strong>Lassen</strong></td>
<td>Apixaban 5 mg/d</td>
<td>157</td>
<td>11.3&lt;sup&gt;17&lt;/sup&gt;</td>
<td>--</td>
<td>--</td>
<td>0</td>
</tr>
<tr>
<td>2007</td>
<td>Enoxaparin 30 mg BID</td>
<td>152</td>
<td>15.6&lt;sup&gt;17&lt;/sup&gt;</td>
<td>--</td>
<td>--</td>
<td>0</td>
</tr>
<tr>
<td>[APROPOS]</td>
<td>RR, p value</td>
<td>153</td>
<td>26.6&lt;sup&gt;17&lt;/sup&gt;</td>
<td>--</td>
<td>--</td>
<td>0</td>
</tr>
</tbody>
</table>

ARR= absolute risk reduction; DVT= Deep vein thrombosis, mos= months, *Mean, NS= Non-significant based on confidence interval, SS= statistically significant based on confidence intervals, VTE= venous thromboembolism
1 Composite of stroke and systemic embolic event in the per-protocol, as-treated population.

2 Values consist of ischemic or uncertain type of stroke

**Treatment of acute DVT and/or Pulmonary Embolism**

*Rivaroxaban.*

**EINSTEIN-DVT trial.** The EINSTEIN-DVT trial was an international, randomized, open-label, assessor-blind, active-controlled, noninferiority, Phase III trial (N=3449). Adults age >18 years with confirmed acute symptomatic DVT, without symptomatic PE, were randomized to rivaroxaban 15 mg twice daily x 3 weeks then 20 mg daily x 3, 6, or 12 months or enoxaparin 1.0 mg/kg twice daily x 5 days transitioning to dose-adjusted VKA (INR: 2.0 to 3.0) x 3, 6, or 12 months.

The primary efficacy outcome (symptomatic recurrent VTE at 6 months) occurred in 2.1% of rivaroxaban–treated patients and 3.0% of enoxaparin/VKA –treated patients (HR: 0.68 [95% CI: 0.44, 1.04], p<0.001). At 12 months, the primary efficacy outcome occurred in 1.3% of rivaroxaban–treated patients and 7.1% of enoxaparin/VKA –treated patients (HR: 0.18 [95% CI: 0.09, 0.39], p<0.001). Clinically relevant bleeding occurred in 8.1% in both treatment groups (p=0.77). Deaths occurred in 2.2% of the rivaroxaban treated group and 2.9% of the enoxaparin group (HR: 0.67 [95% CI: 0.44, 1.02], p=0.02)

These results indicate that rivaroxaban is noninferior at 6 months and superior at 12 months to enoxaparin-plus-warfarin treatment for preventing recurrent DVT (6-month HR 0.68 [95% CI: 0.44, 1.04]; 12-month HR 0.18 [95% CI: 0.09, 0.39]). (39)

**EINSTEIN EXTENSION study.** (40) The EINSTEIN EXTENSION study (40) was an international, randomized, double-blind, placebo-controlled Phase III trial of 1,197 patients. Patients who completed 6 to 12 months of VKA treatment for an acute VTE episode or participated in the Phase III EINSTEIN-DVT or EINSTEIN-PE trials were randomized to rivaroxaban 20 mg daily x 6 to 12 months or placebo.

The primary efficacy outcome (symptomatic recurrent DVT and fatal or non-fatal PE) occurred in 1.3% of rivaroxaban–treated patients and 7.1% of placebo–treated patients (HR: 0.18 [95% CI: 0.09, 0.39], NNT=18). After discontinuation of the study medication, 6 symptomatic recurrent VTE events occurred in each group during a 1-month observation period.

Major bleeding occurred in 4 (0.7%) rivaroxaban–treated patients and in no placebo-treated patients (p=0.106); none of these bleeding events were fatal or in a critical site. Clinically relevant non-major bleeding occurred in 5.4% of rivaroxaban–treated patients and in 1.2% of placebo-treated patients (number needed to harm [NNH]=24).

**EINSTEIN-PE trial.** The EINSTEIN-PE trial was a randomized, open-label, noninferiority trial (N=4,832). Patients with acute symptomatic PE with or without DVT were randomized to rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily or standard therapy with enoxaparin followed by adjusted-dose VKA for 3, 6, or 12 months.

Rivaroxaban was noninferior to standard therapy for the primary efficacy outcome (symptomatic recurrent VTE): The incidence of the primary outcome in the rivaroxaban arm was 2.1% vs.
1.8% in the standard therapy arm (HR1.12 [95% CI: 0.75, 1.68]; noninferiority margin, 2.0; p=0.003).

The principal safety outcome (major or clinically relevant nonmajor bleeding) occurred in 10.3% of patients treated with rivaroxaban and 11.4% treated with standard therapy (HR: 0.90 [95% CI: 0.76, 1.07]; p=0.23). Major bleeding occurred in 1.1% of patients treated with rivaroxaban and 2.2% treated with standard therapy (HR: 0.49 [95% CI: 0.31, 0.79], p=0.003).

This trial demonstrated noninferiority of rivaroxaban to enoxaparin-plus-warfarin treatment over a mean of 9 months of treatment of PE (HR: 1.12 [95% CI: 0.75, 1.68]). (41)

Dabigatran.

RE-COVER trial. The RE-COVER trial was a randomized, double-blind, active-controlled, noninferiority trial in adults (≥18 years) who had acute, symptomatic, objectively verified proximal DVT of the legs or PE randomized to dabigatran (150 mg twice daily, n=1,274) or dose-adjusted warfarin (target INR: 2-3; n=1,265). All patients were initially treated with intravenous (IV) unfractionated heparin or subcutaneous (SC) low-molecular-weight heparin and then switched to assigned therapies.

Results indicated that Dabigatran was non-inferior to dose adjusted warfarin for prevention of recurrent VTE and/or VTE-related death. The rate of the primary outcome in the dabigatran 150 mg group was 2.4% versus 2.1% in the warfarin group, for an absolute difference of 0.4% (95% CI: 0.8, 1.5), p<0.001. The risk of major bleeding was similar between dabigatran and warfarin, with an incidence of 1.6% in the dabigatran 150 mg group, versus 1.9% in the warfarin group (HR: 0.82, 95% CI: 0.45, 1.48). (42)

Conclusions. The EINSTEIN trials have reported that rivaroxaban is superior to warfarin at one year or longer for preventing recurrent events in patients presenting with acute DVT, and noninferior to warfarin for patients presenting with acute PE. In the main EINSTEIN trials, there was no evidence for higher bleeding rates in the rivaroxaban groups, but there was a higher bleeding risk reported for the EINSTEIN-EXTENSION study. The RECOVER trial reported that dabigatran was noninferior to warfarin for treatment of acute DVT, and bleeding risks were not significantly different between groups.

### Table 5 - RCTs for the Treatment of Acute DVT and/or Pulmonary Embolism

<table>
<thead>
<tr>
<th>Study/year</th>
<th>F/UGroup</th>
<th>N</th>
<th>Composite outcome (%/yr)</th>
<th>Ischemic Stroke (%/yr)</th>
<th>Hemorrhagic Stroke (%/yr)</th>
<th>Overall Mortality (%/yr)</th>
<th>CV mortality (%/yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bauersachs</td>
<td>Rivaroxaban 15 mg BID for 3 wks, then 20 mg/d</td>
<td>1731</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>2.2</td>
<td>--</td>
</tr>
</tbody>
</table>

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FirstCarolinaCare Insurance Company, Inc. is a wholly-owned subsidiary of
**[EINSTEIN-DVT]**  
Warfarin or other 1718 VKA  
RR, p value -- -- -- 2.9 --  
Rizaroxaban 15 mg BID for 3 2419 -- -- -- 2.4 --  
Buller 2012  
Warfarin, or other VKA for 3, 2413 -- -- -- 2.1 --  
[EINSTEIN-PE]  
RR, p value -- -- -- 1.13, p=0.53  

**Dabigatran**  
Dabigatran 150 mg twice daily 12742.4\(^f\) -- -- 1.6 --  
Schulman 2009  
Warfarin (dose-adjusted) 12652.1\(^f\) -- -- 1.7 --  
[RE-COVER-VTE]  
RR, p value NS -- -- NS --  

**EXTENSION of subjects who completed 6-12 mos of warfarin or other VKA randomized to rivaroxaban or placebo**  

**Rivaroxaban**  
Rivaroxaban 20 mg for 6 or12 mos 602 1.3\(^g\) -- -- 0.2\(^\wedge\) --  
Romualdi 2011  
Placebo 594 7.1\(^g\) -- -- 0.3\(^\wedge\) --  
[EINSTEIN EXTENSION]  
RR, p value 0.18 NS -- -- -- --  

**Secondary Prevention of ACS**
Rivaroxaban.

ATLAS trials. The ATLAS ACS 2–TIMI 51 (14) was an international, randomized, stratified, double-blind, placebo-controlled trial of 15,526 patients. Eligible patients were adults (mean age 62 years) with symptoms suggestive of an ACS who were hospitalized with a diagnosis of ST segment elevation myocardial infarction (STEMI), non-ST segment elevation myocardial infarction (non-STEMI), or unstable angina. Patients were stabilized before enrollment, with initial management (e.g., revascularization) completed. Patients were randomized to rivaroxaban 2.5 mg, rivaroxaban 5.0 mg, or placebo twice daily in addition to standard anti-platelet therapy with a maximum follow-up of 31 months.

In the twice daily 2.5-mg dose group, the cumulative incidence of the primary efficacy endpoint (death from cardiovascular causes, myocardial infarction (MI), or stroke) was 9.1% vs. 10.7% in the placebo group (HR: 0.84 [95% CI: 0.72, 0.97]; p value=0.01). In the twice daily 5.0-mg dose group, cumulative incidence of the primary efficacy endpoint was 8.8% (HR: 0.85 [95% CI: 0.73, 0.98]; p value vs. placebo=0.02).

In the twice daily 2.5-mg dose group, cumulative incidence of the primary safety endpoint (TIMI-defined major bleeding [a decrease in hemoglobin ≥5 g/dL, intracranial hemorrhage, or cardiac tamponade] not related to coronary artery bypass graft surgery [CABG]) was 1.8% vs. 0.6% in the placebo group (p value <0.001). In the twice daily 5.0-mg dose group, cumulative incidence of the primary safety endpoint was 2.4% (p value vs. placebo <0.001).

The ATLAS ACS-TIMI 46 (43) was an international, randomized, stratified, double-blind, placebo-controlled, dose-escalation Phase II trial of 3,491 patients. Adults (mean age 58 years) were enrolled with symptoms suggestive of an ACS for at least 10 minutes at rest, and either a diagnosis of STEMI or a diagnosis of non-STEMI or unstable angina with at least one of the following:

- Raised cardiac enzyme markers
- 1 mm or more ST segment deviation
- A TIMI risk score of 3 or more (44)

Enrollment was stratified on the intent of local investigators to administer a thienopyridine in accordance with their practice guidelines. Within each stratum, several rivaroxaban doses were tested vs. placebo. The duration of active treatment was 6 months with one additional follow-up visit 30 days later.

At the 10-mg once daily dose, there was no difference in the primary efficacy endpoint (time to first episode of death, MI, stroke, or severe recurrent ischemia requiring revascularization) for Stratum 1 (aspirin only; HR: 0.60 [95% CI: 0.28, 1.29]), Stratum 2 (aspirin plus clopidogrel; HR: 0.90 [95% CI: 0.53, 1.54]), or both groups combined (HR: 0.77 [95% CI: 0.50, 1.20]).

At the 10-mg daily dose, the primary safety endpoint (TIMI major and TIMI minor bleeding plus any bleeding requiring medical attention) occurred significantly more often in rivaroxaban–treated patients than in placebo–treated patients. Significantly more bleeding occurred in patients receiving dual antiplatelet therapy without a decrease in the primary efficacy outcome. In both strata, bleeding occurred in a dose-dependent manner: HRs for once daily rivaroxaban compared with placebo were 2.21 (95% CI: 1.25, 3.91) for the 5-mg dose, 3.35 (95% CI: 2.31,
4.87) for the 10-mg dose, 3.60 (95% CI: 2.32, 5.58) for the 15-mg dose, and 5.06 (95% CI: 3.45, 7.42) for the 20-mg dose.

**Apixaban.**

**APPRAISE-2 trial.** (45) The APPRAISE-2 trial was a randomized, double-blind, placebo-controlled clinical trial of 7,392 patients comparing apixaban 5 mg orally twice daily (2.5 mg twice daily in patients with CrCl <40 ml/min), in addition to standard antiplatelet therapy. Inclusion criteria included patients with a recent ACS (STEMI, NSTEMI, or UA within 7 days) and at least 2 of the following additional risk factors for recurrent ischemic events:

- Age ≥65 years
- DM
- MI the previous 5 years
- Cerebrovascular disease
- Peripheral vascular disease

The trial was terminated prematurely after recruitment of 7,392 patients because of an increase in major bleeding events with apixaban in the absence of a counterbalancing reduction in recurrent ischemic events. With a median follow-up of 241 days, the rate of the primary endpoint (cardiovascular death, myocardial infarction, or ischemic stroke) was 13.2 events per 100 patient-years in the apixaban group and 14.0 events per 100 patient-years in the placebo group (HR: 0.95 [95% CI: 0.80, 1.11], p=0.51).

The rate of the primary safety outcome (major bleeding) was 2.4 events per 100 patient-years in the apixaban group and 0.9 events per 100 patient-years in the placebo group (HR: 2.59 [95% CI: 1.50, 4.46], p=0.001). Five fatal bleeding events occurred in the apixaban group and none in the placebo group. The rate of intracranial bleeds was 0.6 per 100 patient-years in the apixaban group and 0.2 in the placebo group (HR: 4.06 [95% CI: 1.15, 14.38], p=0.03).

**Conclusions.** None of the newer agents have FDA-approval for use in ACS. Several trials have evaluated the addition of rivaroxaban or apixaban to anti-platelet agents in patients with ACS. The ATLAS trials have reported that rivaroxaban decreased a composite outcome of death from cardiovascular causes, MI, or stroke, but was also associated with higher risks of major bleeding. One trial of apixaban, the APPRAISE-2 trial, was terminated early due to an increase in bleeding events without any associated improvement in efficacy.

**Table 6 - Secondary Prevention of Acute Coronary Syndrome**

<table>
<thead>
<tr>
<th>Study/year Group</th>
<th>F/U (mos)</th>
<th>N Enrolled</th>
<th>Composite outcome (%)/yr</th>
<th>Ischemic Stroke (%)/yr</th>
<th>Hemorrhagic Stroke (%)/yr</th>
<th>Overall Mortality (%)/yr</th>
<th>Cardiovascular Mortality (%)/yr</th>
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<tbody>
<tr>
<td>Rivaroxaban</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mega</td>
<td></td>
<td>5114</td>
<td>9.1(^x)</td>
<td>1.0(^y)</td>
<td>--</td>
<td>2.9(^y)</td>
<td>2.7(^y)</td>
</tr>
</tbody>
</table>

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FirstCarolinaCare Insurance Company, Inc. is a wholly-owned subsidiary of FirstHealth of the Carolinas, Inc.
Comparative Efficacy of Newer Oral Anticoagulant Drugs

Several authors have conducted indirect analyses to assess comparative efficacy and safety of the new oral anticoagulants. For stroke prevention in atrial fibrillation, Lip et al. made indirect comparisons between the 3 drugs based on the 3 pivotal trials. (46) A weighted average effects analysis comparing the 3 drugs together to warfarin found significantly reduced stroke and systemic embolism (HR: 0.79 [95% CI: 0.71, 0.88], p<0.001), major bleeding (HR: 0.88 [95% CI: 0.81, 0.95], p=0.001), and intracranial hemorrhage (HR: 0.49 [0.40, 0.61], p<0.001) with use of the new oral anticoagulants. Using the Bucher method for indirect comparisons, dabigatran 150 mg reduced the risk of stroke or systemic embolism by 26% compared with rivaroxaban (HR: 0.74 [95% CI: 0.56, 0.97]). Apixaban reduced the risk of major bleeding by 26% compared with dabigatran 150 mg (HR: 0.74 [95% CI: 0.61, 0.91]) and 34% compared with rivaroxaban (HR: 0.66 [95% CI: 0.54, 0.81]). The authors acknowledge potential confounding effects due to differences in patient populations (mean CHADS2 score 3.4 in ROCKET and 2.0 to 2.1 in dabigatran and apixaban trials) and mean time in the therapeutic range for warfarin controls (55% in ROCKET and 62% to 64% in dabigatran and apixaban trials), different definitions of major bleeding used in the trials, and blinded and open-label trial designs. (46)

A meta-analysis by Alves et al. of the 2 ADVANCE TKR trials (ADVANCE-1 and -2) and the phase II APROPOS TKR trial found a 19% reduction in the risk of major and clinically relevant bleeding with apixaban compared to enoxaparin (relative risk: 0.81 [95% CI: 0.67, 0.97], p=0.02). (47) This was compared to a meta-analysis of the 2 RECORD TKR trials (RECORD-3 and -4) and 2 Phase II TKR trials comparing rivaroxaban to enoxaparin, which showed no
difference in bleeding events (relative risk: 1.09 [95% CI: 0.91, 1.30], p=0.36). Statistical heterogeneity was nonsignificant in both analyses ($I^2=0\%$). Meta-analysis of THR trials showed no difference in bleeding. The authors concluded that the risk of bleeding after TKR is lower with apixaban than with rivaroxaban.

Meta-analyses of 16 RCTs and indirect comparisons by Gómez-Outes et al. were based on the trials reviewed here pooled with phase II trials for both THR and TKR. (48) For the outcome of clinically relevant bleeding, the risk with rivaroxaban was greater than with apixaban (relative risk: 1.52 [95% CI: 1.19, 1.95]), and the risk with apixaban was less than with dabigatran (relative risk: 0.73 [95% CI: 0.57, 0.94]). In contrast, a network meta-analysis of 43 RCTs by Cohen et al. found no significant difference in risk of bleeding (major, clinically relevant, or both) between the drugs. (49) Efficacy outcomes evaluated in these meta-analyses differed. For the outcome of symptomatic VTE, indirect comparison revealed no difference between treatments. (48) For the outcome of all VTE and all-cause mortality (the primary efficacy outcome in the pivotal trials), apixaban was favored over dabigatran and comparable to rivaroxaban for both THR and TKR. (49) Indirect comparison of rivaroxaban and dabigatran for this outcome by Loke et al. indicated superiority of rivaroxaban over dabigatran (relative risk: 0.50 [95% CI: 0.37, 0.68]) and no significant difference in major and clinically relevant bleeding (relative risk: 1.14 [95% CI: 0.80, 1.64]) for pooled THR and TKR in 9 trials. (50) This analysis excluded the RECORD 2 THR trial because of unequal duration of anticoagulation and the RENOVATE II THR trial because it was not completed at the time of the report. These indirect comparisons are summarized in Table 7. A recent comparative effectiveness review by the Agency for Healthcare Research and Quality (AHRQ) concluded that “the balance of benefits to harms for factor Xa inhibitors or DTIs [direct thrombin inhibitors] compared with LMWHs [low molecular-weight heparins] seems favorable” based predominantly on evidence of moderate strength. (51)

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Outcome</th>
<th>Indirect Comparison</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohen 2012</td>
<td>43</td>
<td>Major or clinically relevant bleeding or both</td>
<td>Apixaban v dabigatran v rivaroxaban</td>
<td>No difference between treatments</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All VTE and all-cause mortality</td>
<td>Apixaban v dabigatran</td>
<td>Apixaban favored after both TKR and THR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Apixaban v rivaroxaban</td>
<td>No difference</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clinically relevant bleeding</td>
<td>Apixaban v rivaroxaban</td>
<td>Apixaban favored for pooled THR and TKR</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>Symptomatic VTE</td>
<td>Apixaban v dabigatran v rivaroxaban</td>
<td>No difference between treatments</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Apixaban favored after TKR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• No difference after THR</td>
</tr>
<tr>
<td>Alves 2011</td>
<td>12</td>
<td>Major and clinically relevant bleeding</td>
<td>Apixaban v rivaroxaban</td>
<td>No difference</td>
</tr>
<tr>
<td>Loke 2011</td>
<td>9</td>
<td>Major and clinically relevant bleeding</td>
<td>Rivaroxaban v</td>
<td>No difference</td>
</tr>
</tbody>
</table>
Summary

For stroke prevention in atrial fibrillation, randomized controlled trials (RCTs) have reported that all three agents are non-inferior to warfarin. The rates of bleeding were mixed in these trials in comparison to warfarin, but the majority of trials have reported similar rates of overall bleeding and lower rates for intracranial hemorrhage. Some recent guidelines have favored one of the newer anticoagulants over warfarin as first-line treatment. Based on this evidence and specialty society guidelines, rivaroxaban and dabigatran may be considered medically necessary as an alternative to warfarin treatment for stroke prevention in atrial fibrillation.

For patients undergoing total hip replacement (THR) or total knee replacement (TKR) surgery, rivaroxaban was superior to low molecular-weight (LMW) heparin in clinical trials but also had a higher rate of major bleeding events. Dabigatran was noninferior to LMW heparin with no significant increase in major bleeding events. Based on this evidence and specialty guidelines, rivaroxaban and dabigatran may be considered medically necessary for prophylaxis of thromboembolism in patients undergoing THR and TKR surgery.

For patients with acute DVT or pulmonary embolism (PE), rivaroxaban was reported to be noninferior or superior to warfarin in the EINSTEIN and EINSTEIN-PE trials in reducing the rates of recurrent thromboembolism. Rates of clinically significant bleeding for rivaroxaban in these trials were similar or lower than warfarin. Based on the results of these trials and the FDA-approval of rivaroxaban for this indication, rivaroxaban may be considered medically necessary for treatment of acute DVT and PE. Apixaban has also shown similar efficacy to the other agents in some trials, but increased bleeding rates in others without significant benefit. Apixaban does not yet have FDA-approval for any indication and is therefore considered investigational for all indications.

There is a lack of direct evidence on the comparative efficacy of these newer agents. Indirect comparisons based on the published trials have not consistently shown superiority of one agent over another. This evidence is insufficient for determining comparative efficacy of the newer agents.

Each of the new oral anticoagulants is being evaluated for other off-label uses, including secondary prevention of acute coronary syndromes (ACSs), and thromboprophylaxis in medically ill patients. The FDA is currently reviewing rivaroxaban for the secondary prevention of ACS and apixaban for the prevention of stroke and systemic embolism in atrial fibrillation (AF). These other off-label indications are considered investigational.

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.
Responses were received from 9 academic medical centers and 2 specialty societies. There was near uniform agreement for the medically necessary and investigational indications as written in the policy statements. There was mixed input concerning whether the newer medications should be preferred as first-line agents over warfarin.

**Practice Guidelines and Position Statements**

*Prevention of Stroke and Systemic Embolism in Patients with AF*

Recent evidence-based guidelines published by the American College of Chest Physicians (ACCP), the American Heart Association (AHA) jointly with the American Stroke Association (ASA), the Canadian Cardiovascular Society, and the European Society of Cardiology recommend a risk-stratified approach to the use of anticoagulant therapy in AF patients. For patients at intermediate or high risk of stroke, ACCP guidelines include a weak recommendation based on moderate-quality evidence (Grade 2B) for the use of dabigatran 150 mg twice daily over adjusted-dose warfarin therapy based on greater net clinical benefit shown with dabigatran in the pivotal RE-LY trial. However, caution is advised due to the lack of an antidote for dabigatran and performance in clinical practice that may differ from that in the trial setting because of “less-restricted patient selection” and reduced adherence to “unmonitored drug.” Continuation of warfarin in patients whose international normalized ratio (INR) is maintained in the therapeutic range and who are satisfied with treatment is supported. Recommendations about rivaroxaban and apixaban are not included in the ACCP guidelines because neither drug was FDA-approved at the time the guidelines were written.

Based on Level B evidence (a single RCT or nonrandomized studies), current AHA/ASA guidelines include Class I recommendations for dabigatran and apixaban and a Class IIa recommendation for rivaroxaban as alternatives to warfarin for the prevention of first and recurrent stroke in patients with nonvalvular AF. However, guideline developers note:

1. Long-term efficacy and safety data for these drugs are lacking.
2. Because of their short half-lives (approximately 12 hours), patients who miss doses may be at increased risk for thromboembolism.
3. For patients transitioning from warfarin, the risk of thromboembolism may be increased during the transition period.
4. It is unknown whether patients treated with these agents who experience an acute ischemic stroke can be treated safely with a thrombolytic agent (i.e., tissue-type plasminogen activator) if they are otherwise eligible.

In 2012, the Canadian Cardiovascular Society published a focused update of its guidelines for stroke prevention and rate/rhythm control in AF. The update incorporated findings from the ROCKET AF, RE-LY, AVERROES, and ARISTOTLE trials. These trials were considered high-quality evidence. The guidelines include strong recommendations for oral anticoagulant therapy in patients at high risk of stroke (CHADS$_2$ ≥2) and most patients at intermediate risk of stroke (CHADS$_2$ = 1). A conditional (i.e., weak) recommendation is made for the use of rivaroxaban, dabigatran, or apixaban (if approved by Health Canada) over warfarin when oral anticoagulant therapy is indicated. Based in part on this review, CADTH currently recommends the new oral anticoagulants, dabigatran and rivaroxaban, for stroke prevention in patients with nonvalvular AF in whom warfarin is indicated who have a CHADS$_2$ score ≥2 but cannot maintain adequate anticoagulation with warfarin.
The European Society of Cardiology published a focused update of its AF guidelines in 2012. Based on the 3 trials that directly compared the new oral anticoagulants to warfarin (ROCKET AF, RE-LY, and ARISTOTLE), rivaroxaban, dabigatran, or apixaban (pending approval) is recommended over adjusted-dose warfarin for most patients who require oral anticoagulation (CHA\textsubscript{2}DS\textsubscript{2}-VASc $\geq$ 2 [class I recommendation based on multiple RCTs and general agreement] or CHAD\textsubscript{2}DS\textsubscript{2}-VASc = 1 [class IIa recommendation based on multiple RCTs without general agreement]). Women younger than 65 years with CHAD\textsubscript{2}DS\textsubscript{2}-VASc = 1 for sex category should not be treated (class IIa recommendation based on large non-randomized studies without general agreement). No recommendation is made for one newer oral anticoagulant over another.

**Prophylaxis of Venous Thromboembolism in Patients Undergoing Knee or Hip Replacement Surgery**

Evidence-based guidelines published by the American Academy of Orthopedic Surgeons (AAOS) in 2011 (56) and by the American College of Chest Physicians (ACCP) in 2012 (38, 57) support VTE prophylaxis using pharmacological treatments and/or mechanical compressive devices in patients undergoing THR and TKR. In developing its guidelines, the AAOS did not accept DVT as a surrogate for PE, thus limiting the evidence for specific prophylactic treatments. As summarized by Eikelboom et al.:

“Both guideline panels accepted prevention of fatal PE as the most important goal of thromboprophylaxis. However, the ACCP included asymptomatic (and symptomatic) DVT detected by venography as a measure of the efficacy of thromboprophylaxis, whereas the AAOS rejected DVT (both asymptomatic and symptomatic) as a valid outcome because the panelists considered the link between DVT and PE in patients undergoing hip or knee surgery to be unproven. Thus the AAOS only accepted symptomatic PE and fatal PE as valid outcomes and limited their analysis to studies reporting this outcome.” (10)

Current AAOS Guidelines suggest the use of pharmacologic agents and/or mechanical compressive devices for VTE prophylaxis in patients undergoing elective THR or TKR whose risk of VTE or bleeding is not elevated above that of the surgery itself. (Grade of Recommendation: Moderate)

- However, due to inconclusive evidence, no specific recommendations for the choice or duration of prophylactic regimen are made.
- Consensus recommendations (based on expert opinion) include the use of pharmacologic prophylaxis and mechanical compressive devices in patients who have had a prior VTE, and use of mechanical compressive devices in patients with a known bleeding disorder (e.g., hemophilia) and/or active liver disease.

Current ACCP Guidelines include strong recommendations based on moderate quality evidence (Grade 1B) for a minimum of 10 to 14 days prophylaxis with LMWH, fondaparinux, apixaban, dabigatran, rivaroxaban, low-dose unfractionated heparin, adjusted-dose vitamin K antagonist (VKA), or aspirin in patients with no increased bleeding risk. For patients who decline or are uncooperative with injections or an intermittent pneumatic compression device, apixaban or dabigatran (alternatively rivaroxaban or adjusted-dose VKA if apixaban or dabigatran are unavailable) rather than alternative forms of prophylaxis is recommended.

**Ongoing Trials**
Rivaroxaban

Among ongoing studies of rivaroxaban listed at online site ClinicalTrials.gov, 2 are investigating the use of antidotes for the new oral anticoagulants [NCT01656330, NCT01478282]. Other indications include heparin-induced thrombocytopenia, knee arthroscopy, and hip fracture. These and other ongoing trials of rivaroxaban are listed below.

- A Study to Assess the Effects of 2 Different Prothrombin Complex Concentrates on the Pharmacodynamics of Rivaroxaban in Healthy Adult Volunteers [NCT01656330]
- Reversal of the Antithrombotic Action of New Oral Anticoagulants: REVANT [NCT01478282]
- Rivaroxaban for Treatment of Patients With Suspected or Confirmed Heparin-Induced Thrombocytopenia [NCT01598168]
- Exploring the Efficacy and Safety of Rivaroxaban to Support Elective Percutaneous Coronary Intervention: X-PLORER [NCT01442792]
- Superficial Vein Thrombosis (SVT) Treated With Rivaroxaban Versus Fondaparinux [NCT01499953]
- Efficacy of Rivaroxaban for Prevention of Venous Thromboembolism After Knee Arthroscopy: ERIKA [NCT01629381]
- Treatment of an Acute Deep Vein Thrombosis (DVT) With Either Rivaroxaban or Current Standard of Care Therapy: XALIA [NCT01619007]
- Rivaroxaban Safety Profile in the Prophylaxis of Venous Thromboembolism After Hip Fracture Surgery [NCT01509118]

Dabigatran

There is an ongoing exploratory Phase II trial (RE-ALIGN (58), NCT01452347) comparing a new dose regimen of dabigatran to warfarin in patients who have undergone (less than 3 months before inclusion in the trial) or are currently undergoing (during the current hospital stay) a mechanical bileaflet valve implantation. Similar to the RE-LY trial, RE-ALIGN trial uses a prospective, randomized, open-label, blinded-endpoint (PROBE) design. Target recruitment is 405 patients randomized to dabigatran and warfarin in a 2:1 ratio. The initial dose of dabigatran in the RE-ALIGN trial will range from 150 mg twice daily to 300 mg twice daily and will be initiated based on estimated CrCl. The dose will then be adjusted to achieve steady state trough plasma dabigatran levels of at least 50 ng/mL. This dosing regimen more closely matches the higher target INR required by patients with mechanical heart valves who are treated with warfarin. This and other trials listed at online site ClinicalTrials.gov for novel uses of dabigatran are listed below.

- Dabigatran Etxilate in Patients With Mechanical Heart Valves: RE-ALIGN [NCT01452347]
- Management of Myocardial Injury After Noncardiac Surgery Trial: MANAGE [NCT01661101]
- Dabigatran Versus Warfarin Anticoagulation Before and After Catheter Ablation for the Treatment of Atrial Fibrillation [NCT01607359]
Dabigatran for Peri Procedural Anticoagulation During Radiofrequency Ablation of Atrial Fibrillation: DAPPAR AF [NCT01468155]

Apixaban

ClinicalTrials.gov currently lists a Phase I dose-ranging, pharmacokinetic/pharmacodynamic trial of apixaban in pediatric patients (age 37 weeks to 17 years) with an indwelling central venous catheter (NCT01195727).

Medicare National Coverage

None

References:


53. Furie KL, Goldstein LB, Albers GW et al; on behalf of the American Heart Association Stroke Council, Council on Quality of Care and Outcomes Research, Council on Cardiovascular Nursing, Council on Clinical Cardiology, and Council on Peripheral


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