Formulary Drug Reviews

Apixaban

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Each month, subscribers to *The Formulary Monograph Service* receive 5 to 6 well-documented monographs on drugs that are newly released or are in late phase 3 trials. The monographs are targeted to Pharmacy & Therapeutics Committees. Subscribers also receive monthly 1-page summary monographs on agents that are useful for agendas and pharmacy/nursing in-services. A comprehensive target drug utilization evaluation/medication use evaluation (DUE/MUE) is also provided each month. With a subscription, the monographs are sent in print and are also available on-line. Monographs can be customized to meet the needs of a facility. A drug class review is now published monthly with *The Formulary Monograph Service*. Through the cooperation of *The Formulary, Hospital Pharmacy* publishes selected reviews in this column. For more information about *The Formulary Monograph Service*, call *The Formulary* at 800-322-4349. The June 2013 monograph topics are dimethyl fumarate (BG-12) delayed-release capsules, canagliflozin, ospemifene, aripiprazole extended-release injectable, and dabrafenib. The DUE/MUE is on dimethyl fumarate.

Generic Name:	Apixaban
Proprietary Name:	Eliquis (Bristol-Myers Squibb/Pfizer)
Approval Rating:	1P
Therapeutic Class:	Oral Direct Factor Xa Inhibitors
Similar Drugs:	Dabigatran, Rivaroxaban, Warfarin
Sound- or Look-Alike Names:	Abacavir, Epirubicin

INDICATIONS

Apixaban is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.¹ The US Food and Drug Administration (FDA)-approved indications for rivaroxaban, dabigatran, and warfarin are compared in Table 1.

Apixaban is also under evaluation for use in the prevention and treatment of venous thromboembolic events (VTEs) and has received approval in Canada

and Europe for the prevention of VTE in patients who have undergone elective total hip- or knee-replacement surgery.² Although also studied in acute coronary syndromes, apixaban is no longer being evaluated for this indication.

CLINICAL PHARMACOLOGY

Apixaban is a direct-acting, selective, reversible oral inhibitor of factor Xa, which is responsible for the conversion of prothrombin (factor II) to thrombin (factor IIa), ultimately leading to thrombus formation and clotting. Apixaban is selective for factor Xa; therefore, thrombin and other downstream clotting factors (eg, IIa, fibrin) are inhibited without affecting factors XIIa, XIa, IXa, or VIIa.^{3,4} Apixaban inhibits free and clot-bound factor Xa and prothrombinase activity.¹

When tested in human plasma, apixaban produced concentration-dependent increases in activated partial thromboplastin time (aPTT), modified plasma thromboplastin (PT), international normalized ratio (INR), and Heptest. The modified PT and the Heptest appear to be 10- to 20-fold more sensitive than aPTT or PT for monitoring the anticoagulant effect of apixaban.⁵ In phase 2 and 3 clinical trials, apixaban did not require laboratory monitoring.⁶⁻¹¹

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Table 1. FDA-approved indications for apixaban, dabigatran, rivaroxaban, and warfarin^{1,31-33,a}

Product	Apixaban	Dabigatran	Rivaroxaban	Warfarin
Mechanism	Direct factor Xa inhibitor	Direct thrombin inhibitor	Direct factor Xa inhibitor	Vitamin K antagonist
FDA-approved indications				
Reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation	X	X	X	
Prophylaxis and treatment of thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement				X
Prophylaxis and treatment of venous thrombosis and its extension, PE				X
Treatment of DVT and PE and for the reduction in the risk of recurrence of DVT and PE			X	
Prevention of DVT, which may lead to PE in patients undergoing hip- or knee-replacement surgery			X	
Reduction of risk of death, recurrent MI, and thromboembolic events after MI				X

Note: DVT = deep vein thrombosis; MI = myocardial infarction; PE = pulmonary embolism.

Apixaban produces several metabolites via cytochrome P450 (CYP-450) 3A4–dependent mechanisms. O-demethyl apixaban sulphate, a nonreactive metabolite, is the primary metabolite produced; therefore, the potential for apixaban to form reactive metabolites is expected to be minimal, and apixaban did not prolong the QTc interval in healthy volunteers.⁵

PHARMACOKINETICS

Following oral administration, peak apixaban concentrations are reached in approximately 3 to 4 hours. The prolonged oral absorption results in an apparent half-life of about 12 hours, despite a clearance half-life of about 6 hours.^{1,12} Absolute bioavailability is approximately 50% for doses up to 10 mg. Food does not affect the bioavailability.^{1,12} Apixaban is absorbed throughout the gastrointestinal (GI) tract, with about 55% of absorption occurring in the distal small bowel and ascending colon.¹ Concentrations increase in a linear, dose-proportional manner at doses up to 10 mg; at doses of 25 mg or greater, dissolution-limited absorption with decreased bioavailability is observed.^{1,12} Plasma protein binding is approximately 87%. The volume of distribution is approximately 21 L.¹

Apixaban is metabolized primarily via CYP3A4 and, to a lesser extent, by CYP1A2, CYP2C8, CYP2C9, CYP2C19, and CYP2J2. Approximately 25% of the apixaban dose is eliminated as metabolites in the

urine and feces. Apixaban is primarily present in the circulation as unchanged drug; there are no active circulating metabolites.^{1,13} Renal excretion accounts for about 27% of total clearance. Biliary and direct intestinal excretion contribute to elimination in the feces.¹

COMPARATIVE EFFICACY

Indications: Reduce the Risk of Stroke and Systemic Embolism in Patients With Nonvalvular Atrial Fibrillation

Guidelines

Guideline: American Heart Association (AHA)/American Stroke Association science advisory on oral antithrombotic agents for the prevention of stroke in nonvalvular atrial fibrillation

Reference: Furie KL, et al, 2012¹⁴

Comments: The guideline acknowledges that warfarin, dabigatran, apixaban, and rivaroxaban are all indicated for the prevention of first and recurrent stroke in patients with nonvalvular atrial fibrillation. The guideline recommends that selection of an agent be individualized on the basis of risk factors, cost, tolerability, patient preference, potential for drug interactions, and time in INR therapeutic range if the patient has been taking warfarin. Dabigatran and apixaban are both listed as alternatives to warfarin in patients with nonvalvular atrial fibrillation and 1 additional stroke risk factor.

Rivaroxaban is listed as an alternative to warfarin in patients with nonvalvular atrial fibrillation who are at moderate to high risk of stroke due to a prior history of transient ischemic attack (TIA), stroke, or systemic embolism or the presence of 2 or more additional stroke risk factors. The guideline also lists apixaban as an alternative to aspirin in patients for whom warfarin therapy is deemed unsuitable.

Studies

Drug: Apixaban vs Warfarin

Reference: Granger CB, et al, 2011; Lopes RD, et al, 2010 (ARISTOTLE trial)^{1,10,15}

Study Design: Randomized, double-blind, double-dummy, multicenter, noninferiority study

Study Funding: Bristol-Myers Squibb, Pfizer

Patients: 18,201 patients with atrial fibrillation and at least 1 of the following additional risk factors for stroke: prior stroke, TIA, or systemic embolism; age 75 years or older; arterial hypertension requiring treatment; diabetes mellitus; heart failure of at least New York Heart Association class II; or left ventricular ejection fraction of 40% or less. Mean age was 69 years and the mean CHADS₂ score was 2.1. The population was 65% male, 83% White, and 14% Asian; 40% were enrolled in Europe, 25% in North America, 19% in Latin America, and 16% in Asia. There was a history of stroke, TIA, or non-central nervous system (CNS) systemic embolism in 19% of patients. Prior to study entry, 43% of patients were vitamin K antagonist therapy-naïve.

Intervention: Apixaban 5 mg orally twice daily (or 2.5 mg twice daily in subjects with at least 2 of the following characteristics: age 80 years or older, body weight 60 kg or less, or serum creatinine 1.5 mg/dL or greater) or warfarin dosed to a target INR of 2 to 3. All patients were to be treated for a minimum of 1 year; median duration of follow-up was 1.8 years.

Results:

Primary Endpoint(s):

- Stroke (ischemic or hemorrhagic) or systemic embolism: 212 patients with apixaban (1.27% per year) and 265 patients with warfarin (1.6% per year) meeting noninferiority (primary endpoint) and superiority (secondary endpoint) criteria (hazard ratio [HR], 0.79; 95% confidence interval [CI], 0.66 to 0.95; $P < .001$ for noninferiority; $P = .01$ for superiority).

Secondary Endpoint(s):

- All-cause mortality: 603 patients with apixaban (3.52% per year) and 669 patients with warfarin

(3.94% per year) (HR, 0.89; 95% CI, 0.8 to 0.99; $P = .047$).

- Stroke, systemic embolism, or death from any cause: 752 patients with apixaban (4.49% per year) and 837 patients with warfarin (5.04% per year) (HR, 0.89; 95% CI, 0.81 to 0.98; $P = .02$).
- Myocardial infarction (MI): 90 patients with apixaban (0.53% per year) and 102 patients with warfarin (0.61% per year) (HR, 0.88; 95% CI, 0.66 to 1.17).
- Stroke, systemic embolism, MI, or death from any cause: 810 patients with apixaban (4.85% per year) and 906 patients with warfarin (5.49% per year) (HR, 0.88; 95% CI, 0.8 to 0.97; $P = .01$).
- Pulmonary embolism (PE) or deep vein thrombosis (DVT): 7 patients with apixaban (0.04% per year) and 9 patients with warfarin (0.05% per year) (HR, 0.78; 95% CI, 0.29 to 2.1).
- Major bleeding: 2.13% per year with apixaban and 3.09% per year with warfarin (HR, 0.69, 95% CI, 0.6 to 0.8; $P < .001$).

Other Endpoint(s):

- Stroke: 199 patients with apixaban (1.19% per year) and 250 patients with warfarin (1.51% per year) (HR, 0.79; 95% CI, 0.65 to 0.95; $P = .01$).
- Ischemic stroke without hemorrhage: 140 patients with apixaban (0.83% per year) and 136 patients with warfarin (0.82% per year) (HR, 1.02; 95% CI, 0.81 to 1.29).
- Ischemic stroke with hemorrhagic conversion: 12 with apixaban (0.07% per year) and 20 with warfarin (0.12% per year) (HR, 0.6; 95% CI, 0.29 to 1.23).
- Hemorrhagic stroke: 40 with apixaban (0.24% per year) and 78 with warfarin (0.47% per year) (HR, 0.51; 95% CI, 0.35 to 0.75; $P < .001$).
- Systemic embolism: 15 with apixaban (0.09% per year) and 17 with warfarin (0.1% per year) (HR, 0.87; 95% CI, 0.44 to 1.75).
- Net clinical outcome (stroke, systemic embolism, major bleeding or death from any cause): 1,009 patients with apixaban (6.13% per year) and 1,168 patients with warfarin (7.2% per year) (HR, 0.85; 95% CI, 0.78 to 0.92; $P < .001$).

Comments: Patients in the warfarin group had an INR in the therapeutic range for a median of 66% of the time and a mean of 62.2% of the time, excluding INR values during the first 7 days and during study drug interruptions. Results were consistent across major subgroups including weight,

CHADS₂ score, prior warfarin use, level of renal impairment, geographic region, apixaban dose, type of atrial fibrillation, and aspirin use at randomization. Results were also consistent across patient risk of stroke and bleeding.¹⁶

Drug: Apixaban vs Aspirin

Reference: Connolly S, et al, 2011 (AVERROES trial)^{1,17-19}

Study Design: Randomized, double-blind, superiority study

Study Funding: Bristol-Myers Squibb, Pfizer

Patients: 5,599 patients with nonvalvular atrial fibrillation for whom warfarin therapy was unsuitable; mean age 70 years, 59% male, 14% with a prior stroke or TIA.

Intervention: Apixaban 5 mg orally twice daily (or 2.5 mg twice daily in selected patients) or aspirin 81 to 324 mg orally once daily; mean follow-up of 1.1 years.

Results:

Primary Endpoint(s):

- Composite outcome of stroke or systemic embolism: 51 patients with apixaban (1.6% per year) and 113 patients with aspirin (3.7% per year) (HR, 0.45; 95% CI, 0.32 to 0.62; $P < .001$).
- Major bleeding: 44 events (1.4% per year) with apixaban and 39 events (1.2% per year) with aspirin (HR, 1.13; 95% CI, 0.74 to 1.75; $P = .57$).

Secondary Endpoint(s):

- All-cause mortality: 111 patients with apixaban (3.51% per year) and 140 patients with aspirin (4.42% per year) (HR, 0.79; 95% CI, 0.62 to 1.02; $P = .068$).

Other Endpoint(s):

- Ischemic stroke: 35 patients (1.1% per year) with apixaban and 93 patients (3% per year) with aspirin (HR, 0.37; 95% CI, 0.25 to 0.55; $P < .001$).
- Hemorrhagic stroke: 6 patients with apixaban (0.19% per year) and 9 patients with aspirin (0.28% per year) (HR, 0.67; 95% CI, 0.24 to 1.88; $P = .45$).
- Systemic embolism: 2 patients with apixaban (0.06% per year) and 13 patients with aspirin (0.41% per year) (HR, 0.15; 95% CI, 0.03 to 0.68; $P = .01$).
- MI: 24 patients with apixaban (0.76% per year) and 28 patients with aspirin (0.89% per year) (HR, 0.86; 95% CI, 0.5 to 1.48; $P = .59$).
- Vascular death: 84 patients with apixaban (2.65% per year) and 96 patients with aspirin

(3.03% per year) (HR, 0.87; 95% CI, 0.65 to 1.17; $P = .37$).

- Hospitalization for cardiovascular cause: 367 patients (12.6%) with apixaban and 455 patients (15.9%) with aspirin (HR, 0.79; 95% CI, 0.69 to 0.91; $P < .001$).
- Efficacy and safety in patients with renal impairment (estimated glomerular filtration rate less than 45 mL/min/1.73 m²): Primary events occurred in 1.8% per year with apixaban and 5.6% per year with aspirin (HR, 0.32; 95% CI, 0.18 to 0.55; $P < .001$) and major bleeding occurred in 2.5% per year with apixaban and 2.2% per year with aspirin (HR, 1.2; 95% CI, 0.65 to 2.1).
- Clinically relevant nonmajor bleeding: 3.1% per year with apixaban and 2.7% per year with aspirin (HR, 1.15; 95% CI, 0.86 to 1.54; $P = .35$).

Comments: The study was discontinued when a prespecified interim analysis revealed a significant reduction in stroke and systemic embolism for apixaban compared with aspirin and a modest increase in major bleeding. Bleeding sites did not differ between treatment groups. Rates of both stroke and bleeding increased with higher CHADS₂ scores; however, apixaban maintained its reduced relative risk of stroke and bleeding risk irrespective of CHADS₂ score.

Indication: Venous Thromboembolic Event Prophylaxis in Patients Undergoing Total Hip- or Knee-Replacement Surgery
Guidelines

Guideline: Prevention of VTE in orthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines

Reference: Falck-Ytter Y, et al, 2012²⁰

Comments: The guideline recommends prophylaxis for a minimum of 10 to 14 days with low-molecular-weight heparin (LMWH), fondaparinux, apixaban, dabigatran, rivaroxaban, low-dose heparin, adjusted-dose warfarin, aspirin, or an intermittent pneumatic compression device (IPCD) following total hip- or knee-replacement surgery. Use of an LMWH is preferred over the other pharmacologic alternatives. Combined prophylaxis with a pharmacologic agent and IPCD is recommended during the hospital stay. IPCD use alone is preferred in patients with increased bleeding risk. Apixaban or dabigatran is recommended for patients declining or uncooperative

with injections or an IPCD; rivaroxaban or warfarin is suggested if apixaban and dabigatran are unavailable. Prophylaxis should be extended for up to 35 days from the day of surgery.

Studies

Drug: Apixaban vs Enoxaparin and Warfarin

Reference: Lassen MR, et al, 2007 (APROPOS study)⁶

Study Design: Randomized, double-blind, double-dummy, multicenter study

Study Funding: Bristol-Myers Squibb

Patients: 1,238 patients undergoing elective total knee replacement.

Intervention: Apixaban 5, 10, or 20 mg/day administered as a single- or twice-daily divided dose; enoxaparin 30 mg twice daily; or open-label warfarin (titrated to a desired INR of 1.8 to 3). The study was conducted in a blind, double-dummy fashion with regard to apixaban and enoxaparin, while the warfarin arm was open-label. Enoxaparin or matching placebo injections began 12 to 24 hours after skin wound closure on a 12-hour dosing schedule. Apixaban tablets or matching placebo were administered starting 12 to 24 hours after skin wound closure, and open-label warfarin was administered from the evening of the day of surgery. The duration of treatment was 10 to 14 days and was initiated 12 to 24 hours after surgery in the apixaban and enoxaparin groups and on the evening of surgery in the warfarin group. Bilateral venography was performed between days 10 and 14.

Results:

Primary Endpoint(s):

- Composite of adjudicated asymptomatic and symptomatic DVT, nonfatal PE, or death from any cause during the intended treatment period: 9% with apixaban 2.5 mg twice daily and 11.3% with apixaban 5 mg once daily compared with 15.6% with enoxaparin and 26.6% with warfarin.
- Major bleeding during the treatment period or within 2 days after the last dose of study medication: 0% to 3.3% in the apixaban treatment groups compared with 0% in the enoxaparin and warfarin treatment groups; a clear dose effect on total bleeding rates was noted in the apixaban group. This effect was irrespective of once-daily or divided twice-daily dosing and consistent with a total daily dose effect.

Secondary Endpoint(s): See Table 2.

Comments: Overall, all apixaban groups had lower primary efficacy event rates than either comparator,

and the incidence of the primary outcome decreased with increased apixaban doses. Rates of major bleeding events were infrequent.

Limitations: The primary objective of the study was to evaluate safety and efficacy of apixaban and to investigate dose-response relationships. However, the study was not designed to detect differences for efficacy between once-daily and divided twice-daily dosing.

Drug: Apixaban vs Enoxaparin

Reference: Lassen MR, et al, 2009 (ADVANCE-1 trial)⁷

Study Design: Randomized, double-blind, double-dummy, multicenter, noninferiority and superiority study

Study Funding: Bristol-Myers Squibb, Pfizer

Patients: 3,195 patients undergoing total knee-replacement surgery.

Intervention: Apixaban 2.5 mg orally twice daily ($n = 1,599$) or enoxaparin 30 mg subcutaneously twice daily ($n = 1,596$). Therapy was initiated 12 to 24 hours after completion of surgery and continued for 10 to 14 days. Bilateral venography was performed between days 10 and 14. Patients were followed for 60 days after anticoagulation therapy was stopped.

Results:

Primary Endpoint(s):

- Composite of asymptomatic and symptomatic DVT, nonfatal PE, and death from any cause during treatment: 9% with apixaban and 8.8% with enoxaparin (relative risk [RR], 1.02; 95% CI, 0.78 to 1.32; $P = .06$ for noninferiority).

Secondary Endpoint(s):

- Composite of proximal DVT, nonfatal PE, VTE-related death, or death from any cause during treatment: 2% with apixaban and 1.6% with enoxaparin (RR, 1.25; 95% CI, 0.7 to 2.23).
- Composite of symptomatic DVT and PE during treatment: 1.2% with apixaban and 0.8% with enoxaparin (RR, 1.46; 95% CI, 0.72 to 2.95).
- Major bleeding: 0.7% with apixaban and 1.4% with enoxaparin ($P = .053$).
- Composite incidence of major bleeding and clinically relevant nonmajor bleeding: 2.9% with apixaban and 4.3% with enoxaparin ($P = .03$).

Comments: Apixaban did not meet the prespecified statistical criteria for noninferiority compared with enoxaparin for efficacy of thromboprophylaxis after knee replacement, but it did have a lower rate of clinically relevant bleeding.

Table 2. Efficacy and safety outcomes during the treatment period in the APROPOS study for prevention of venous thromboembolic events following elective total knee replacement^a

	Apixaban 2.5 mg twice daily	Apixaban 5 mg daily	Apixaban 5 mg twice daily	Apixaban 10 mg daily	Apixaban 10 mg twice daily	Apixaban 20 mg daily	Enoxaparin 30 mg twice daily	Warfarin (INR, 1.8 to 3)
Asymptomatic DVT	8.3%	11.3%	4.8%	10.5%	4.5%	7.3%	12.8%	25.7%
Symptomatic DVT	0.9%	0%	0%	1.9%	0%	0%	0.9%	0.9%
PE	0%	0%	0%	0%	0.9%	0.9%	1.8%	0%
Major bleeding	0%	2.6%	2.6%	0.6%	2.6%	3.3%	0%	0%
All bleeding	3.9%	3.3%	6.5%	7.1%	9.8%	9.9%	5.4%	5.3%
Total VTEs	9%	11.3%	4.8%	12.4%	5.5%	8.2%	15.6%	26.6%

Note: DVT = deep vein thrombosis; INR = international normalized ratio; PE = pulmonary embolism; VTEs = venous thromboembolic events.

Limitations: Efficacy endpoint events occurred less frequently than predicted.

Reference: Lassen MR, et al, 2010 (ADVANCE-2 study)⁸

Study Design: Randomized, double-blind, double-dummy, multicenter, noninferiority and superiority study

Study Funding: Bristol-Myers Squibb, Pfizer

Patients: 3,057 patients undergoing elective unilateral or bilateral total knee replacement.

Intervention: Apixaban 2.5 mg orally twice daily or enoxaparin 40 mg subcutaneously once daily. The first dose of apixaban was initiated 12 to 24 hours after completion of surgery and enoxaparin was initiated 12 hours before the surgery. Both drugs were continued for 10 to 14 days postsurgery. Bilateral venography was performed between days 10 and 14.

Results:

Primary Endpoint(s):

- Composite of asymptomatic and symptomatic DVT, nonfatal PE, and all-cause mortality during treatment: 15% with apixaban and 24% with enoxaparin (RR, 0.62; 95% CI, 0.51 to 0.74; 1-sided $P < .001$ for noninferiority and superiority; absolute risk reduction was 9.3%; 95% CI, 4.8 to 12.7; 1-sided $P < .001$ for noninferiority).
- Major bleeding during treatment: 0.6% with apixaban and 0.9% with enoxaparin (absolute risk difference, -0.33% ; 95% CI, -0.95 to 0.29 ; $P = .301$).

Secondary Endpoint(s):

- Composite of asymptomatic or symptomatic proximal DVT, nonfatal PE, and VTE-related

death during treatment: 1.09% with apixaban and 2.17% with enoxaparin (RR, 0.5; 95% CI, 0.26 to 0.97; $P = .019$ for superiority).

- Composite of symptomatic DVT, nonfatal PE, and VTE-related death during treatment: 0.46% with apixaban and 0.46% with enoxaparin.
- All DVT during treatment: 14.6% with apixaban and 24.4% with enoxaparin.
- Symptomatic DVT during treatment: 0.2% with apixaban and 0.46% with enoxaparin.
- Proximal DVT during treatment: 0.76% with apixaban and 2.17% with enoxaparin.
- PE, nonfatal or fatal, during treatment: 0.26% with apixaban and 0% with enoxaparin.
- All-cause mortality during treatment: 0.13% with apixaban and 0% with enoxaparin.
- Symptomatic DVT during follow-up: 0.14% with apixaban and 0.07% with enoxaparin.
- PE during follow-up: 0.21% with apixaban and 0.07% with enoxaparin.
- Death during follow-up: 0.07% in both groups.

Other Endpoint(s):

- Clinically relevant nonmajor bleeding: 2.9% with apixaban and 3.8% with enoxaparin (absolute risk difference, -0.91% ; 95% CI, -2.2 to 0.38 ; $P = .167$).
- Major or clinically relevant nonmajor bleeding: 3.5% with apixaban and 4.8% with enoxaparin (absolute risk difference, -1.24% ; 95% CI, -2.66 to 0.18 ; $P = .088$).
- All bleeding events: 6.9% with apixaban and 8.4% with enoxaparin (absolute risk difference, -1.39% ; 95% CI, -3.29 to 0.51 ; $P = .141$).

Comments: Oral apixaban was shown to be superior to subcutaneous enoxaparin for the primary endpoint; the frequency of major bleeding events did not differ between the 2 treatment groups.

Limitations: Venography was not available for assessment in 35% of patients compared with the 30% predicted.

Reference: Lassen MR, et al, 2010 (ADVANCE-3 study)²¹

Study Design: Randomized, double-blind, double-dummy, multicenter, noninferiority and superiority study

Study Funding: Bristol-Myers Squibb, Pfizer

Patients: 5,407 patients undergoing elective total hip replacement.

Intervention: Apixaban 2.5 mg orally twice daily or enoxaparin 40 mg subcutaneously once daily. The first dose of apixaban was initiated 12 to 24 hours after completion of surgery and enoxaparin was initiated 12 hours before the surgery. Both drugs were continued for 32 to 38 days postsurgery, after which bilateral venography was performed.

Results:

Primary Endpoint(s):

- Composite of asymptomatic or symptomatic DVT, nonfatal PE, or all-cause mortality during treatment: 1.4% with apixaban and 3.9% with enoxaparin (RR, 0.36; 95% CI, 0.22 to 0.54; 1-sided $P < .001$ for noninferiority and 2-sided $P < .001$ for superiority).
- Major bleeding during the treatment period: 0.8% with apixaban and 0.7% with enoxaparin (absolute difference, 0.1%; 95% CI, -0.3 to 0.6; $P = .54$); major bleeding with onset after the first dose of apixaban occurred in 0.3% of patients.

Secondary Endpoint(s):

- Composite of asymptomatic or symptomatic proximal DVT, nonfatal PE, or all-cause mortality during treatment: 0.5% with apixaban and 1.1% with enoxaparin (RR, 0.4; 95% CI, 0.15 to 0.8; 1-sided $P < .001$ for noninferiority and 2-sided $P = .01$ for superiority).

Other Endpoint(s):

- Symptomatic VTE or death from VTE: 0.1% with apixaban and 0.4% with enoxaparin (RR, 0.4; 95% CI, 0.01 to 1.28; $P = .11$).
- Composite of major and clinically relevant non-major bleeding: 4.8% with apixaban and 5%

with enoxaparin (absolute difference, -0.2; 95% CI, -1.4 to 1; $P = .72$); major or clinically relevant nonmajor bleeding with onset after the first dose of apixaban occurred in 3.6% of patients.

- All bleeding event: 11.7% with apixaban and 12.6% with enoxaparin ($P = .34$).

Comments: Oral apixaban was shown to be superior to subcutaneous enoxaparin for the primary endpoint; the frequency of major bleeding events did not differ between the 2 treatment groups.

Limitations: Sample size was increased following a planned interim analysis, when the observed event rate was lower than had been predicted.

Indication: Venous Thromboembolic Event Prophylaxis in Medically Ill Patients Guidelines

Guideline: Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines

Reference: Guyatt GH, et al, 2012²²

Comments: In hospitalized patients with acute medical illness (congestive heart failure, severe respiratory disease, or confined to bed with 1 or more additional VTE risk factors), current guideline recommends an LMWH, low-dose heparin, or fondaparinux for VTE prophylaxis. If anticoagulant thromboprophylaxis is contraindicated, mechanical prophylaxis is recommended. The guideline recommends against prophylaxis for acutely ill medical patients at low risk of thrombosis.

Studies

Drug: Apixaban vs Enoxaparin

Reference: Goldhaber SZ, et al, 2011 (ADOPT trial)²³

Study Design: Randomized, double-blind, double-dummy, multicenter study

Study Funding: Bristol-Myers Squibb, Pfizer

Patients: 6,528 patients with congestive heart failure or respiratory failure or other medical disorders and at least 1 additional risk factor for VTE who were hospitalized with an expected stay of at least 3 days.

Intervention: Apixaban 2.5 mg orally twice daily for 30 days or enoxaparin 40 mg subcutaneously once daily for 6 to 14 days; mean duration of exposure was 24.9 days in the apixaban group and 7.3 days in the enoxaparin group. Bilateral

compression ultrasonography was conducted on day 30.

Results:

Primary Endpoint(s):

- 30-day composite of death related to VTE, PE, symptomatic DVT, or asymptomatic proximal-leg DVT: 2.71% with apixaban and 3.06% with enoxaparin (RR, 0.87; 95% CI, 0.62 to 1.23; $P = .44$); secondary endpoints were to be examined for noninferiority only if superiority was established for the primary efficacy endpoint.
- Major bleeding through day 30: 0.47% with apixaban and 0.19% with enoxaparin (RR, 2.58; 95% CI, 1.02 to 7.24; $P = .04$).

Secondary Endpoint(s):

- Composite of total VTE and death related to VTE until parenteral treatment was discontinued: 1.73% with apixaban and 1.61% with enoxaparin (RR, 1.06; 95% CI, 0.69 to 1.63).
- Death from any cause: 4.1% in each group.

Other Endpoint(s):

- Nonmajor bleeding plus clinically relevant nonmajor bleeding: 2.67% with apixaban and 2.08% with enoxaparin (RR, 1.28; 95% CI, 0.93 to 1.76; $P = .12$).
- All bleeding: 7.73% with apixaban and 6.81% with enoxaparin (RR, 1.13; 95% CI, 0.95 to 1.34; $P = .18$).
- MI: No difference.
- Stroke: No difference.
- Thrombocytopenia: No difference.

Comments: An extended course of apixaban prophylaxis in medically ill hospitalized patients was not superior to enoxaparin and was associated with an increase in incidence of major bleeding events.

Limitations: Event rates in the enoxaparin group were lower than predicted. Ultrasonography was performed in only 64% of patients; however, in clinical practice it is rarely performed in asymptomatic patients.

Indication: Venous Thromboembolic Event Treatment Guidelines

Guideline: Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines

Reference: Kearon C, et al, 2012²⁴

Comments: The guideline advocates use of short-term LMWH, unfractionated heparin, or fondaparinux for initial treatment of most DVT or PE, with LMWH or fondaparinux generally preferred.

Warfarin is generally recommended for long-term therapy, initiated concomitantly with the initial treatment, except in patients with cancer for whom LMWH is preferred to warfarin. Warfarin and LMWH were given a weak recommendation over dabigatran and rivaroxaban because of the limited information available on the newer agents. Apixaban was not addressed in the current guidelines.

Studies

Drug: Apixaban vs Placebo

Reference: Agnelli G, et al, 2012 (AMPLIFY-EXT trial)²⁵

Study Design: Randomized, double-blind, multicenter study

Study Funding: Bristol-Myers Squibb, Pfizer

Patients: 2,486 patients who had completed 6 to 12 months of anticoagulation therapy following DVT or PE and for whom treating health care providers were uncertain about continuing anticoagulation therapy; randomization was stratified by initial diagnosis (DVT or PE) and participation or no participation in the AMPLIFY acute treatment study.

Intervention: Apixaban 2.5 or 5 mg orally twice daily or placebo for 12 months.

Results:

Primary Endpoint(s):

- Symptomatic recurrent VTE or death from any cause: 3.8% with apixaban 2.5 mg (RR, 0.33; 95% CI, 0.22 to 0.48; $P < .001$), 4.2% with apixaban 5 mg (RR, 0.36; 95% CI, 0.25 to 0.53; $P < .001$), and 11.6% with placebo.
- Major bleeding 0.2% with apixaban 2.5 mg, 0.1% with apixaban 5 mg, and 0.5% with placebo (not statistically different).

Secondary Endpoint(s):

- Symptomatic recurrent VTE or VTE-related death: 1.7% with apixaban 2.5 mg (RR, 0.19; 95% CI, 0.11 to 0.33), 1.7% with apixaban 5 mg (RR, 0.2; 95% CI, 0.11 to 0.34; $P < .001$), and 8.8% with placebo.
- Composite of symptomatic recurrent VTE, VTE-related death, MI, stroke, or cardiovascular disease-related death: 2.1% with apixaban 2.5 mg (RR, 0.21; 95% CI, 0.13 to 0.35), 2.3% with apixaban 5 mg (RR, 0.23; 95% CI, 0.14 to 0.38), and 10% with placebo.
- Major bleeding or clinically relevant nonmajor bleeding: 3.2% with apixaban 2.5 mg, 4.3% with apixaban 5 mg, or 2.7% with placebo (not statistically different).

Other Endpoint(s):

- Clinically relevant nonmajor bleeding: 3% with apixaban 2.5 mg, 4.2% with apixaban 5 mg, and 2.3% with placebo (not statistically different).
- Death from any cause: 0.8% with apixaban 2.5 mg, 0.5% with apixaban 5 mg, and 1.7% with placebo.
- VTE, VTE-related death, MI, stroke, cardiovascular-disease related death, or major bleeding (reduction represents net clinical benefit): 2.4% with apixaban 2.5 mg (RR, 0.23; 95% CI, 0.14 to 0.37), 2.5% with apixaban 5 mg (RR, 0.24; 95% CI, 0.15 to 0.38), and 10.4% with placebo.

Comments: Extended anticoagulation with apixaban reduced the risk of recurrence compared with placebo, without increasing the incidence of major bleeding. An ongoing trial (AMPLIFY) is comparing apixaban for 6 months with enoxaparin followed by warfarin for 6 months for the treatment of patients with DVT or PE.²

Limitations: This study was not a comparison of extended anticoagulation with apixaban and warfarin or an LMWH.

Drug: Apixaban vs LMWH

Reference: Buller H, et al, 2008⁹

Study Design: Randomized, open-label, multicenter, dose-ranging study

Study Funding: Bristol-Myers Squibb

Patients: 520 patients with symptomatic DVT.

Intervention: Apixaban 5 mg orally twice daily (130 patients), apixaban 10 mg orally twice daily (134 patients), apixaban 20 mg orally once daily (128 patients), or tinzaparin 175 units/kg once daily or enoxaparin 1.5 mg/kg once daily or 1 mg/kg twice daily subcutaneously, or fondaparinux followed by adjusted-dose vitamin K antagonist to maintain INR between 2 and 3 (128 patients); duration of therapy was 84 to 91 days. Study was double-blind to apixaban dose and open-label for comparator regimens.

Results:

Primary Endpoint(s):

- Composite of symptomatic recurrent VTE and asymptomatic deterioration in the thrombotic burden as assessed by repeat bilateral compression ultrasonography or perfusion lung scan: 6% with apixaban 5 mg twice daily, 5.6% with apixaban 10 mg twice daily, 2.6% with apixaban 20 mg once daily (4.7% with any apixaban dose), and 4.2% with LMWH/vitamin K antagonist (no significant differences).

- Composite of major and clinically relevant non-major bleeding: 8.6% with apixaban 5 mg twice daily, 4.5% with apixaban 10 mg twice daily, 8.9% with apixaban 20 mg once daily (7.3% with any apixaban dose), and 7.9% with LMWH/vitamin K antagonist (no significant differences).

Secondary Endpoint(s):

- All-cause mortality: 2.3% with apixaban 5 mg twice daily, 0.7% with apixaban 10 mg twice daily, 0.8% with apixaban 20 mg once daily, and 0% with LMWH/vitamin K antagonist (all deaths were in patients with underlying malignant disease; 1 death in the apixaban 20 mg group was due to possible PE; the other deaths in the apixaban group were due to progressive malignant disease [n = 3] or suicide [n = 1]).

Comments: Not designed to establish noninferiority or superiority of apixaban to the control. This small dose-ranging study was designed with a sample size sufficient to estimate differences between apixaban and the control group to within approximately 10%.

Indication: Coronary Syndromes**Guidelines**

Guideline: 2013 American College of Cardiology Foundation (ACCF)/AHA guideline for the management of ST-elevation myocardial infarction

Reference: O'Gara PT, et al, 2013²⁶

Comments: Current guidelines for the management of ST-segment elevation MI (STEMI) recommend antiplatelet therapy with aspirin and a P2Y₁₂ such as clopidogrel, prasugrel, or ticagrelor with the initial reperfusion therapy and continued for up to 1 year. Additional medical therapies may include beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aldosterone antagonists, and HMG-CoA reductase inhibitors. The use of oral factor Xa inhibitors is not addressed in the current guidelines.

Guideline: 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/non-ST-elevation myocardial infarction

Reference: Jneid H, et al, 2012²⁷

Comments: Current guidelines for the management of unstable angina/non-STEMI recommend antiplatelet therapy with aspirin and a P2Y₁₂ such as clopidogrel, prasugrel, or ticagrelor or a glycoprotein IIb/IIIa inhibitor such as eptifibatide or tirofiban. Concomitant anticoagulant therapy with unfractionated heparin, enoxaparin, fondaparinux, or bivalirudin is also advised depending on the

management strategy selected. The use of oral factor Xa inhibitors is not addressed in the current guidelines.

Studies

Drug: Apixaban vs Placebo

Reference: Alexander JH, et al, 2009 (APPRAISE trial)¹¹

Study Design: Randomized, double-blind, placebo-controlled, multicenter, dose-ranging study

Study Funding: Bristol-Myers Squibb, Pfizer

Patients: 1,715 patients with recent STEMI or non-STEMI acute coronary syndrome and at least 1 additional risk factor for recurrent ischemic events. **Intervention:** Apixaban (2.5 mg twice daily, 10 mg once daily, 10 mg twice daily, or 20 mg once daily) or placebo for a total of 6 months; nearly all patients were taking aspirin, and 76% of patients were also receiving clopidogrel.

Results:

Primary Endpoint(s):

- Major or clinical relevant nonmajor bleeding: 5.7% with apixaban 2.5 mg twice daily ($P = .09$), 7.9% with apixaban 10 mg once daily ($P = .005$), and 3% with placebo.

Secondary Endpoint(s):

- Composite of cardiovascular death, MI, severe recurrent ischemia, or ischemic stroke: 7.6% with apixaban 2.5 mg twice daily, 6% with apixaban 10 mg once daily, and 8.7% with placebo (difference not significant).

Comments: The 2 highest apixaban dose arms were discontinued following an interim analysis revealing excess total bleeding. Compared with placebo, apixaban resulted in a dose-dependent increase in major or clinically relevant nonmajor bleeding and lower rates of ischemic events. The increase in bleeding was more pronounced and the reduction in ischemic events less evident in patients taking aspirin plus clopidogrel than in those taking aspirin alone.

Reference: Alexander JH, et al, 2011 (APPRAISE-2 trial)²⁸

Study Design: Randomized, double-blind, placebo-controlled, multicenter study

Study Funding: Bristol-Myers Squibb, Pfizer

Patients: 7,392 patients with an acute coronary syndrome (STEMI, non-STEMI, or unstable angina) within the previous 7 days and at least 2 additional risk factors for recurrent ischemic events.

Intervention: Apixaban 5 mg twice daily or placebo in addition to standard antiplatelet therapy (aspirin

or aspirin plus any P2Y₁₂-receptor antagonist); median exposure to the study drug was 175 days for apixaban and 185 days for placebo; median follow-up was 241 days.

Results:

Primary Endpoint(s):

- Composite of cardiovascular death, MI, or ischemic stroke: 7.5% with apixaban (13.2 events per 100 patient-years) and 7.9% with placebo (14 events per 100 patient-years) (HR, 0.95; 95% CI, 0.8 to 1.11; $P = .51$).
- Major bleeding: 1.3% with apixaban (2.4 events per 100 patient-years) and 0.5% with placebo (0.9 events per 100 patient-years) (HR, 2.59; 95% CI, 1.5 to 4.46; $P = .001$).

Secondary Endpoint(s):

- Composite of cardiovascular death, MI, ischemic stroke, or unstable angina: 9.5% with apixaban and 10% with placebo ($P = .43$).
- Composite of cardiovascular death, MI, ischemic or hemorrhagic stroke, or fatal bleeding (net clinical outcome): 8% with apixaban and 8.1% with placebo ($P = .8$).
- Composite of death from any cause, MI, or ischemic or hemorrhagic stroke (net clinical outcome): 8.8% with apixaban and 8.9% with placebo ($P = .9$).

Other Endpoint(s):

- Any bleeding: 18.5% with apixaban and 8.4% with placebo ($P < .001$).

Comments: This trial was terminated early because of increased major bleeding events with apixaban in the absence of a reduction in recurrent ischemic events. Apixaban did not demonstrate a net clinical benefit for this indication.

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

Contraindications

Apixaban is contraindicated in patients with active pathological bleeding and in patients with severe hypersensitivity (eg, anaphylactic reactions) to apixaban or any component of the formulation.¹

Warnings and Precautions

Apixaban labeling contains a black box warning similar to rivaroxaban advising that discontinuing therapy with either agent may place patients with atrial fibrillation at increased risk of thrombotic events. If anticoagulation with apixaban must be discontinued for any reason other than pathological bleeding, coverage with another anticoagulant is strongly advised.¹

Apixaban increases bleeding risk and can cause serious bleeding. Bleeding risk is increased with the concomitant use of drugs affecting hemostasis. Apixaban should be discontinued in patients with active pathological bleeding. The anticoagulant effect of apixaban is irreversible and can be expected to persist for about 24 hours after the last dose. A specific antidote is not available and apixaban is not expected to be dialyzable. Procoagulant reversal agents such as prothrombin complex concentrate, activated prothrombin complex concentrate, or recombinant factor VIIa may be considered but have not been evaluated in clinical studies. Oral activated charcoal reduces the absorption of apixaban.¹

Apixaban has not been studied in patients with prosthetic heart valves; therefore, use is not recommended in this population.¹

The safety and effectiveness of apixaban have not been established in pediatric patients.¹

Apixaban is in Pregnancy Category B. Adverse effects on the fetus were not observed in animal models. Because of the risk of bleeding during pregnancy and delivery, apixaban should only be used during pregnancy if the potential benefit outweighs the potential risk to the mother and fetus.¹

It is not known whether apixaban or its metabolites are excreted in human milk; however, apixaban is excreted in the milk of lactating rats. Women should be advised to discontinue breast-feeding or discontinue apixaban, taking into account the importance of the drug to the mother.¹

Table 3 compares the contraindications, warnings, and precautions for the use of apixaban, dabigatran, rivaroxaban, and warfarin in patients with nonvalvular atrial fibrillation.

ADVERSE REACTIONS

In studies assessing apixaban in patients with atrial fibrillation, bleeding-related adverse events were the most common reason for treatment discontinuation.¹

Bleeding events in the ARISTOTLE study are summarized in **Table 4**. In this trial, apixaban was associated with less major bleeding and less clinically relevant nonmajor bleeding when compared with warfarin in patients with nonvalvular atrial fibrillation. The incidence of intracranial bleeding and fatal bleeding was also lower with apixaban. Major bleeding occurred less with apixaban than warfarin across subgroups including prior warfarin use, gender, weight, stroke history, heart failure, CHADS₂ score, and aspirin use. Significant differences in bleeding

risk between apixaban and warfarin were not observed in patients younger than 65 years, those with diabetes mellitus, those with normal renal function, or those residing in Europe.¹

Hypersensitivity reactions and syncope were reported in less than 1% of patients treated with apixaban.¹

Effects on liver function tests (LFTs) are of special interest in light of previous findings with ximelagatran. Elevation in LFTs has been reported by some patients, but the incidence rate was no different from the comparator groups.⁶⁻⁸

DRUG INTERACTIONS

Apixaban is a substrate for CYP3A4 and P-gp. Inhibitors of CYP3A4 and P-gp increase apixaban exposure and bleeding risk; inducers of CYP3A4 and P-gp decrease apixaban exposure and efficacy. A reduced apixaban dose is advised for patients requiring concomitant therapy with apixaban and a strong dual inhibitor of CYP3A4 and P-gp (eg, ketoconazole, itraconazole, ritonavir, clarithromycin). For patients already receiving a reduced dose, coadministration with a strong dual CYP3A4 and P-gp inhibitor should be avoided. Concomitant use of apixaban with strong dual inducers of CYP3A4 and P-gp (eg, rifampin, carbamazepine, phenytoin, St. John's wort) should be avoided.¹

Bleeding risk is increased with the concomitant use of apixaban with other drugs that affect hemostasis (eg, aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, and nonsteroidal anti-inflammatory drugs).¹

Apixaban does not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2D6, CYP3A4/5, or CYP2C19 activities in complementary DNA-expressed enzyme systems and human liver microsomes, nor does it induce CYP1A2, CYP2B6, or CYP3A4/5 in human hepatocytes. Potential for apixaban to inhibit or induce CYP or P-gp is minimal; therefore, the potential for apixaban to affect the pharmacokinetics of other drugs is expected to be low.^{1,5} Coadministration of apixaban 20 mg orally for 10 days with digoxin did not affect the pharmacokinetic profile of digoxin.^{1,5} Apixaban also did not alter the pharmacokinetics of naproxen, atenolol, or acetylsalicylic acid.¹

RECOMMENDED MONITORING

In major clinical trials, laboratory monitoring of aPTT, PT/INR, and factor Xa levels was not required. However, modified PT and Heptest appear to be 10- to 20-fold more sensitive than aPTT or PT for monitoring the anticoagulant effect of apixaban.⁵ Certain patient

Table 3. Contraindications, warnings, and precautions for use in patients with nonvalvular atrial fibrillation^{1,31-33}

	Apixaban	Dabigatran	Rivaroxaban	Warfarin
Contraindications				
Active pathological bleeding	X	X	X	
Severe hypersensitivity reaction to the product	X	X	X	X
Mechanical prosthetic heart valve		X		
Pregnancy				X ^a
Threatened abortion, eclampsia, and preeclampsia				X
Hemorrhagic tendencies or blood dyscrasia				X
Recent or contemplated surgery of the CNS or eye, or traumatic surgery resulting in large open surfaces				X
Bleeding tendencies associated with active ulceration or overt bleeding of the GI, GU, or respiratory tract; CNS hemorrhage; cerebral aneurysm; dissecting aorta, pericarditis and pericardial effusion; and bacterial endocarditis				X
High potential for noncompliance				X
Spinal puncture and other procedures with potential for uncontrollable bleeding				X
Major regional or lumbar block anesthesia				X
Malignant hypertension				X
Black box warnings				
Increased stroke risk if discontinued	X		X	
Spinal/Epidural hematoma			X	
Major or fatal bleeding				X
Warnings and precautions				
Bleeding risk	X	X	X	X
Increased stroke risk in atrial fibrillation if discontinued	X	X	X	
Patients with prosthetic heart valves	X	X		
Spinal/Epidural hematoma			X	
Pregnancy-related hemorrhage			X	
Interactions with P-gp inducers and inhibitors		X		
Interactions with combined P-gp and CYP3A4 inducers and inhibitors	X ^b		X	
Use in patients with renal impairment			X	

(continued)

Table 3. Contraindications, warnings, and precautions for use in patients with nonvalvular atrial fibrillation^{1,31-33} (CONT.)

	Apixaban	Dabigatran	Rivaroxaban	Warfarin
Use in patients with hepatic impermanent			X	
Tissue necrosis				X
Systemic atheroemboli and cholesterol microemboli				X
Heparin-induced thrombocytopenia				X
Females of reproductive potential				X
Concomitant conditions with increased risk				X
Endogenous factors affecting INR response				X
Special populations				
Hepatic impairment	Caution in moderate impairment; not recommended in severe impairment	No dosage adjustment necessary	Avoid use in moderate or severe impairment, or coagulopathy associated with hepatic disease.	Caution in patients with moderate to severe impairment or coagulopathy associated with hepatic disease.
Renal impairment	Reduce dose in patients with any 2 of the following: SCr $\geq$ 1.5 mg/mL, $\geq$ 80 years of age, body weight $\leq$ 60 kg.	Reduce dose in severe impairment.	Reduce dose in moderate impairment; avoid use in patients with CrCl $<$ 15 mL/min.	No dosage adjustment necessary
Geriatric	No unique precautions	Risk of stroke and bleeding increase with age.	Risk of stroke and bleeding increase with age.	Enhanced response; consider lower initiation and maintenance doses.
Pediatric	Safety and effectiveness are not established.	Safety and effectiveness are not established.	Safety and effectiveness are not established.	Use with caution.
Pregnancy	Use with caution; Category B	Use with caution; Category C	Use with caution; Category C	Contraindicated in nonvalvular atrial fibrillation; Category X
Breast-feeding	Not recommended	Use with caution.	Not recommended	Use with caution.

Note: CNS = central nervous system; CrCl = creatinine clearance; GI = gastrointestinal; GU = genitourinary; INR = international normalized ratio; P-gp = P-glycoprotein; SCr = serum creatinine.

^aExcept in women with a mechanical heart valve.

^bNot included in the warnings and precautions in the product labeling, but a recognized interaction requiring apixaban dosage reduction.

populations (eg, hepatic impairment, low body weight, extreme obesity) may require more frequent laboratory monitoring, but these parameters have not been established in clinical trials.

All trials involved monitoring for elevations in alanine aminotransferase (ALT), aspartate aminotransferase

(AST), and bilirubin, and abnormal bruising/bleeding; however, routine monitoring of liver function tests is not required. Any changes to medications, such as additional anticoagulation agents, or potential for drug-drug interactions should be monitored, though potential for drug-drug interactions is anticipated to be minimal.

Table 4. Bleeding events in patients with nonvalvular atrial fibrillation in the ARISTOTLE study^{1,15}

	Apixaban (n = 9,088)	Warfarin (n = 9,052)	Hazard ratio (95% CI)	P
Major bleeding	327 (2.13% per year)	462 (3.09% per year)	0.69 (0.6 to 0.8)	< .001
GI	128 (0.83% per year)	141 (0.93% per year)	0.89 (0.7 to 1.14)	—
Intracranial	52 (0.33% per year)	122 (0.8% per year)	0.41 (0.3 to 0.57)	< .001
Intraocular	32 (0.21% per year)	22 (0.14% per year)	1.42 (0.83 to 2.45)	—
Fatal	10 (0.06% per year)	37 (0.24% per year)	0.27 (0.13 to 0.53)	—
Clinically relevant nonmajor bleeding	318 (2.08% per year)	444 (3% per year)	0.7 (0.6 to 0.8)	< .001

Note: GI = gastrointestinal.

DOSING

The recommended apixaban dosage for patients with atrial fibrillation is 5 mg orally twice daily. A reduced dosage of 2.5 mg orally twice daily is recommended for patients with any 2 of the following characteristics: age 80 years or older, body weight 60 kg or less, or SCr 1.5 mg/dL or greater. The reduced 2.5 mg twice daily dosage is also advised for

patients receiving concomitant therapy with drugs that are strong dual inhibitors of CYP3A4 and P-gp.¹ Clinical trials assessed dosages ranging from 5, 10, and 20 mg once daily to 2.5, 5, 10, and 20 mg twice daily.⁶⁻¹¹

Apixaban, dabigatran, rivaroxaban, and warfarin dosing in nonvalvular atrial fibrillation is compared in Table 5.

Table 5. Comparative dosing in nonvalvular atrial fibrillation^{1,31-33}

	Apixaban	Dabigatran	Rivaroxaban	Warfarin
Usual dosage	5 mg orally twice daily	150 mg orally twice daily	20 mg orally once daily	Adjusted based on INR response to target INR of 2.5 (range, 2 to 3); typically 2 to 10 mg once daily
Special instructions	Lower dose in patients with any 2 of the following: age $\geq$ 80 years of age, body weight $\leq$ 60 kg, SCr $\geq$ 1.5 mg/dL	Do not break, crush, or chew capsules.	Take with evening meal.	Genotype may inform initial dose selection; monitor INR daily until stable in therapeutic range, then give every 1 to 4 weeks.
Dose in renal impairment	2.5 mg orally twice daily if SCr $\geq$ 1.5 mg/dL and 1 additional risk factor	75 mg orally twice daily if CrCl 15 to 30 mL/min	15 mg orally once daily if CrCl 15 to 50 mL/min	No dosage adjustment necessary
Dose in hepatic impairment	No dosage adjustment necessary in mild impairment; avoid use in severe impairment	No dosage adjustment necessary	Avoid use in moderate or severe impairment.	Impaired synthesis of clotting factors and decreased metabolism of warfarin; dose adjusted to INR results

Note: CrCl = creatinine clearance; INR = international normalized ratio; SCr = serum creatinine.

Apixaban should be discontinued at least 48 hours before elective surgery or invasive procedures with moderate or high risk of clinically important bleeding. It should be discontinued at least 24 hours before elective surgery or invasive procedures with a low risk of bleeding or where bleeding could be easily managed.¹

When converting patients from warfarin to apixaban, warfarin should be discontinued and apixaban started when the INR is below 2. When switching from apixaban to warfarin, discontinue apixaban and begin a parenteral anticoagulant and warfarin at the time the next dose of apixaban would have been taken. The parenteral anticoagulant should be discontinued when the INR reaches an acceptable range. When switching between apixaban and anticoagulants other than warfarin, discontinue one and begin the other at the next scheduled dose.¹

PRODUCT AVAILABILITY

Apixaban received FDA approval on December 28, 2012.²⁹ It is available as 2.5 and 5 mg tablets supplied in bottles of 60 and 180 tablets and hospital unit-dose blister packages of 100 tablets.¹ Apixaban tablets should be stored at controlled room temperature (20°C to 25°C [68°F to 77°F]), with excursions permitted between 15°C and 30°C (59°F and 86°F).¹

DRUG SAFETY/RISK EVALUATION AND MITIGATION STRATEGY (REMS)

Apixaban was approved with a REMS including a communication plan.^{29,30}

CONCLUSION

Apixaban is an oral agent that is able to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. Fewer major bleeding events and clinically relevant nonmajor bleeding events were reported with apixaban versus warfarin in the ARISTOTLE trial. Laboratory monitoring of aPTT, PT/INR, and factor Xa levels was not useful in monitoring the anticoagulation effect of apixaban. The anticoagulant effect of apixaban is irreversible and can be expected to persist for about 24 hours after the last dose. A specific antidote is not available, and apixaban is not expected to be dialyzable. Procoagulant reversal agents such as prothrombin complex concentrate, activated prothrombin complex concentrate, or recombinant factor VIIa may be considered, but have not been evaluated in clinical studies.

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Continuing Education Case Study Quiz

Goal—The goal of this program is to educate pharmacists about the use of apixaban for the prevention of stroke in patients with nonvalvular atrial fibrillation.

Objectives—At the completion of this program, the reader will be able to:

1. Describe the pharmacology and pharmacokinetics of apixaban.
2. Discuss the risks associated with the use of apixaban.
3. Discuss the potential benefit of apixaban for an individual patient.
4. Apply the information on the use of apixaban to a case study.

Key Words—atrial fibrillation, factor Xa inhibitors, new drugs

1. The US Food and Drug Administration (FDA)–approved indication for apixaban is to:
 - a. Reduce the risk of recurrent deep vein thrombosis (DVT) or pulmonary embolism (PE).
 - b. Reduce the risk of postoperative thrombosis.
 - c. Reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.
 - d. Treat acute DVT.
2. Apixaban inhibits which of the following:
 - a. Free factor Xa.
 - b. Clot-bound factor Xa.
 - c. Prothrombinase activity.
 - d. All of the above.
3. Food affects the bioavailability of apixaban:
 - a. True
 - b. False
4. Apixaban is primarily metabolized via:
 - a. CYP1A2
 - b. CYP2C9
 - c. CYP2D6
 - d. CYP3A4
5. In the ARISTOTLE study, what was the rate of stroke or systemic embolism in the apixaban treatment group?
 - a. 1.1% per year
 - b. 1.27% per year
 - c. 1.6% per year
 - d. 3.7% per year
6. Apixaban was approved with a risk evaluation and mitigation strategy (REMS) including a communication plan.
 - a. True
 - b. False
7. Apixaban is in Pregnancy Category:
 - a. A.
 - b. B.
 - c. C.
 - d. X.
8. In clinical trials, the most common reason for the discontinuation of apixaban therapy was:
 - a. Bleeding.
 - b. Elevations in alanine aminotransferase (ALT) or aspartate aminotransferase (AST).
 - c. Nausea.
 - d. Vomiting.
9. Compared with warfarin in the ARISTOTLE study, apixaban was associated with:
 - a. Increased mortality, but a reduced incidence of major bleeding.
 - b. Reduced incidence of stroke or systemic embolism, but an increased incidence of major bleeding.
 - c. Reduced incidence of stroke or systemic embolism and a reduced incidence of major bleeding.
 - d. Equivalent risk of stroke or systemic embolism, but a reduced incidence of major bleeding.

10. The labeling for which agent contains a black box warning regarding an increased stroke risk upon discontinuation?
- Apixaban
 - Dabigatran
 - Fondaparinux
 - Warfarin

Case History

GC is an 85-year-old female, weighing 60 kg, with a history of high blood pressure, osteoarthritis, and nonvalvular atrial fibrillation. She is currently taking hydrochlorothiazide 12.5 mg once a day, diltiazem extended-release 360 mg once daily, acetaminophen extended-release 650 mg 3 times daily as needed, and warfarin 5 mg every Monday, Wednesday, and Friday. She dislikes getting her international normalized ratio (INR) checked and has difficulty regularly attending appointments at the anticoagulation clinic; therefore her prescriber has elected to switch her warfarin therapy to apixaban.

11. What is the recommended dose of apixaban for GC?
- 2.5 mg once a day
 - 2.5 mg twice daily
 - 5 mg once daily
 - 5 mg twice daily
12. Upon discontinuing GC's warfarin therapy, when should apixaban therapy be initiated?
- When her next warfarin dose was due
 - 24 hours after discontinuing warfarin
 - 48 hours after discontinuing warfarin
 - When the INR drops below 2
13. When GC picks up her apixaban prescription at her pharmacy, she asks the pharmacist if she has to monitor the amount of vitamin K she consumes daily. Which of the following is the best response?
- She should avoid products containing vitamin K to the best of her ability.
 - She still needs to consume a consistent amount of vitamin K.
 - She does not need to worry about the amount of vitamin K in her diet.
 - She should increase her vitamin K consumption.
14. After several months of apixaban therapy, GC has scheduled gall bladder surgery. She should be instructed to temporarily discontinue apixaban how long before the procedure?

- At least 7 days
- At least 48 hours
- At least 24 hours
- At least 12 hours

15. After a year on apixaban therapy, GC has been diagnosed with *Helicobacter pylori* infection, and her doctor prescribes a regimen including clarithromycin, omeprazole, and amoxicillin. Which of the following is the preferred course of action?
- An alternative *H. pylori* regimen should be recommended.
 - Her apixaban dose should be decreased with the initiation of clarithromycin.
 - Her apixaban dose should be increased with the initiation of omeprazole.
 - No change in therapy is necessary with the addition of this triple-drug regimen.

This CE activity is co-sponsored by ProCE, Inc. and Hospital Pharmacy. ProCE, Inc. is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. ACPE Universal Activity Number 0221-9999-13-033-H01-P has been assigned to this knowledge-based home-study CE activity (initial release date 06-01-13).

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