# *Therapeutic Class Overview*
# *Oral Anticoagulants*

**Therapeutic Class**

- **Overview/Summary:** Apixaban (Eliquis®), dabigatran etexilate mesylate (Pradaxa®), edoxaban tosylate (Savaysa®), rivaroxaban (Xarelto®) and warfarin (Coumadin®, Jantoven®) are oral anticoagulants that are Food and Drug Administration (FDA)-approved for various cardiovascular indications.[1-4] Warfarin, has been the principle oral anticoagulant for more than 60 years and has extensive, well established data demonstrating its safety and efficacy in all of its FDA-approved indications.[6-8] Apixaban, edoxaban tosylate and rivaroxaban are selective factor Xa inhibitors while dabigatran etexilate mesylate is a direct thrombin inhibitor (DTI). The newer novel oral anticoagulants are approved to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF).[1-4] Apixaban, dabigatran etexilate mesylate and rivaroxaban are also approved for the treatment and prophylaxis deep vein thrombosis (DVT) and pulmonary embolism (PE), whereas edoxaban tosylate has approval for the treatment of DVT and PE. Dabigatran etexilate is approved for DVT and PE prophylaxis after hip replacement surgery. Additionally, apixaban and rivaroxaban are indicated for DVT prophylaxis which may lead to PE in patients undergoing knee or hip replacement surgery.[1-4] Apixaban, edoxaban tosylate and rivaroxaban are selective factor Xa inhibitors while dabigatran etexilate mesylate is a direct thrombin inhibitor. The evidence demonstrating the efficacy of warfarin for FDA-approved indications, including reducing the risk of stroke and systemic embolism in patients with AF, is well established, and warfarin has been considered the standard of care in high-risk patients with AF.[10] While the data for apixaban, dabigatran etexilate mesylate, edoxaban tosylate and rivaroxaban are not as substantial as compared to warfarin, the newer oral anticoagulants are associated with several advantages. Unlike warfarin, apixaban, dabigatran etexilate mesylate, edoxaban tosylate and rivaroxaban are not associated with a narrow therapeutic window, numerous drug-drug and -food interactions, or monitoring requirements.[11,12] Apixaban and dabigatran etexilate mesylate require twice-daily dosing for all FDA-approved indications, in comparison to edoxaban tosylate and warfarin which are only administered once daily. Rivaroxaban is dosed once daily for all indications except for the treatment of DVT and PE, for which it is dosed twice daily. It is also recommended to give rivaroxaban with food, specifically with the evening meal for AF patients.[1-5] Of all the oral anticoagulants, only warfarin does not require a dosage adjustment in patients with renal impairment. Lower doses are recommended for apixaban, dabigatran etexilate mesylate, edoxaban tosylate and rivaroxaban (in AF only).[1-5] Moreover, apixaban requires a dosage adjustment when two or more of the following factors are present: age ≥80 years, weight ≤60 kg or serum creatinine ≥1.5 mg/dL.[1] In situations where a major bleed occurs, no specific antidote is currently available for the new oral anticoagulants.[12]

**Table 1. Current Medications Available in the Therapeutic Class**[1-4]

| Generic (Trade Name) | Food and Drug Administration-Approved Indications | Dosage Form/Strength | Generic Availability |
|---|---|---|---|
| Apixaban (Eliquis®) | DVT/PE prophylaxis* and treatment, DVT prophylaxis following hip or knee replacement surgery, to reduce the risk of stroke and systemic embolism in nonvalvular atrial fibrillation | Tablet:<br>2.5 mg<br>5 mg | - |
| Dabigatran etexilate mesylate (Pradaxa®) | DVT/PE prophylaxis‡ and treatment†, to reduce the risk of stroke and systemic embolism in nonvalvular atrial fibrillation, DVT/PE prophylaxis following hip replacement surgery | Capsule:<br>75 mg<br>110 mg<br>150 mg | - |
| Enoxaban tosylate (Savaysa®) | DVT/PE treatment†, to reduce the risk of stroke and systemic embolism in | Tablet:<br>15 mg | - |

| Generic (Trade Name) | Food and Drug Administration-Approved Indications | Dosage Form/Strength | Generic Availability |
|---|---|---|---|
| | nonvalvular atrial fibrillation | 30 mg<br>60 mg | |
| Rivaroxaban (Xarelto®) | DVT/PE prophylaxis* and treatment, DVT prophylaxis following hip or knee replacement surgery, to reduce the risk of stroke and systemic embolism in nonvalvular atrial fibrillation | Tablet:<br>10 mg<br>15 mg<br>20 mg | - |
| Warfarin (Coumadin®*, Jantoven®*) | DVT/PE prophylaxis and treatment, to reduce the risk of death, recurrent MI, and thromboembolic events after an MI, prophylaxis and treatment of thromboembolic complication associated with atrial fibrillation and/or cardiac valve replacement | Tablet:<br>1 mg<br>2 mg<br>2.5 mg<br>3 mg<br>4 mg<br>5 mg<br>6 mg<br>7.5 mg<br>10 mg | ✔ |

DVT=Deep Vein Thrombosis, MI=myocardial infarction, PE=pulmonary embolism
*Indicated to reduce the risk of recurrent DVT or PE following initial six months of treatment for DVT/PE.
†Indicated for treatment of DVT and PE in patients who have been treated with a parenteral anticoagulant for five to 10 days.
‡Indicated to reduce the risk of recurrent DVT or PE in patients who have been previously treated.

**Evidence-based Medicine**

- As it has been the principle oral anticoagulant for more than 60 years, the clinical evidence derived from meta-analyses and Cochrane Reviews demonstrating the safety and efficacy of warfarin in Food and Drug Administration-approved indications is well established.[10,12-18]
- The safety and efficacy of the oral anticoagulants have been evaluated in many clinical trials.[19-64]
- The efficacy of apixaban in patients with nonvalvular atrial fibrillation (AF) was evaluated in the AVERROES and ARISTOTLE trials.[19,23]
- In ARISTOTLE (N=18,201), patients were randomized to receive apixaban 5 mg twice daily or dose-adjusted warfarin (to target an International Normalized Ratio [INR] of 2.0 to 3.0). The incidence of stroke or systemic embolism, the primary endpoint, was significantly reduced in patients treated with apixaban compared to patients treated with warfarin (1.27 vs 1.60% per year; HR, 0.79; 95% CI, 0.66 to 0.95; *P*<0.001 for non inferiority and *P*=0.01 for superiority).
    - Treatment with apixaban was associated with a significantly lower incidence of major intracranial bleeding (*P*<0.001), and major bleeding at other locations (*P*=0.004) compared to warfarin treatment. There was no difference in the rate of major gastrointestinal bleeding with apixaban compared to warfarin (*P*=0.37). The rate of myocardial infarction (MI) was similar between the apixaban and warfarin treatment groups (*P*=0.37); however, apixaban treatment significantly reduced death from any cause compared to warfarin treatment (3.52 vs 3.94% per year; HR, 0.89; 95% CI, 0.80 to 0.998; *P*=0.047).[19]
- In AVERROES (N=5,599), patients were randomized to receive apixaban 5 mg twice daily or aspirin 81 to 324 mg once daily. The incidence of stroke or systemic embolism, the primary endpoint, was significantly reduced in patients treated with apixaban compared to patients treated with aspirin (1.6 vs 3.7% per year; hazard ratio [HR], 0.45; 95% confidence interval [CI], 0.32 to 0.62; *P*<0.001).
- There was no difference in major bleeding between the apixaban and aspirin treatment groups (*P*=0.57). The incidences of intracranial bleeding (*P*=0.69), extracranial bleeding (*P*=0.42), gastrointestinal bleeding (*P*=0.71), non gastrointestinal bleeding (*P*=0.22) and fatal bleeding (*P*=0.53) were similar between the treatment groups.[23]
- Approval of apixaban for use as prophylaxis of DVT and PE in patients who have undergone hip or knee replacement surgery, was established after being compared to enoxaparin in three large, multi-

centered, double-blind, double-dummy, randomized control trials: ADVANCE-1, ADVANCE-2, and ADVANCE-3.[44-46]

- In ADVANCE-1, the statistical criterion for the noninferiority of apixaban as compared with twice-daily administration of enoxaparin was not met. DVT, non-fatal PE, and all-cause death occurred in 104 of 1157 patients (9.0%) in the apixaban group, as compared with 100 of 1130 patients (8.8%) in the enoxaparin group (relative risk [RR], 1.02; 95% CI, 0.78 to 1.32; P=0.06 for noninferiority; difference in risk, 0.1%; 95% CI, –2.2 to 2.4; P<0.001).[44]
- In ADVANCE-2, apixaban was had statistically significant reduction in risk compared to enoxaparin once-daily for prevention of all VTE and all-cause death (RR, 0.62; 95% CI, 0.51 to 0.74, one-sided P<0.0001 when tested for non-inferiority and for superiority). Absolute risk reduction was 9.3% (95% CI, 5.8% to 12.7%) in favor of apixaban (one-sided P<0.0001 for non-inferiority).[44]
- In ADVANCE-1, There was a statistically significant increase in major and non-major bleeding for twice daily enoxaparin 30 mg compared to apixaban (adjusted difference in event rates according to type of surgery, -0.81%; 95% CI, -1.49% to −0.14%; P=0.053) as opposed to ADVANCE-2, where there was no difference in major bleeding rates between enoxaparin daily and apixaban (P=0.3014).[44,45]
- In ADVANCE-3 there was a statistically significant reduction in asymptomatic or symptomatic DVT, nonfatal PE, or death from any cause with apixaban 2.5 mg twice dialy compared with enoxaparin 40 mg daily (RR with apixaban, 0.36; 95% CI, 0.22 to 0.54; one-sided P<0.001 for noninferiority and two-sided P<0.001 for superiority). The absolute risk reduction with apixaban was 2.5% (95% CI, 1.5% to 3.5%).[46]

- Approval of dabigatran etexilate mesylate for use in AF was based on the clinical evidence derived from the non inferiority, RE-LY trial (N=18,113). After a median follow-up of two years, dabigatran etexilate mesylate 110 mg twice-daily was associated with a similar rate of stroke and systemic embolism compared to warfarin (*P*=0.34), while dabigatran etexilate mesylate 150 mg twice-daily was associated with a significantly lower rate (*P*<0.001). Rates of major bleeding were similar between warfarin and dabigatran etexilate mesylate 150 mg twice-daily (*P*=0.31) but significantly less with dabigatran etexilate mesylate 110 mg twice-daily (*P*=0.003).[26]
  - No differences were observed between the two treatments with regard to death from any cause and pulmonary embolism (PE); however, the rate of MI was significantly higher (*P*=0.048 with dabigatran etexilate mesylate 150 mg vs warfarin) and the rate of hospitalization significantly lower (*P*=0.003 with dabigatran etexilate mesylate 110 mg vs warfarin) with dabigatran etexilate mesylate.[30]
  - A 2012 subgroup analysis of RE-LY demonstrated a nonsignificant increase in MI with dabigatran etexilate mesylate compared to warfarin, but other myocardial ischemic events were not increased. In addition, results revealed that treatment effects of dabigatran etexilate mesylate were consistent in patients at higher and lower risk of myocardial ischemic events.[23] In contrast, a meta-analysis published in 2012 demonstrated that dabigatran etexilate mesylate is associated with an increased risk of MI or acute coronary syndrome (ACS) in a broad spectrum of patients (e.g., stroke prophylaxis in AF, acute venous thromboembolism [VTE], ACS, short term prophylaxis of deep venous thrombosis [DVT]) compared to different controls (warfarin, enoxaparin, or placebo).[64]
- The RE-COVER study found dabigatran etexilate mesylate to be noninferior to warfarin in preventing recurrent VTE who had presented with acute symptoms of DVT or PE (P<0.001), with the RE-COVER II study also confirming the results (P<0.001).[47,48] Patients who participated in the RE-COVER or RE-COVER II study and received dabigatran etexilate mesylate and had additional risk factors could elect for long term VTE prophylaxis in two follow up studies, RE-MEDY or RE-SONATE. RE-MEDY was and active-control study whereas RE-SONATE was placebo-controlled. Dabigatran etexilate mesylate was found to be noninferior to warfarin and superior to placebo in long-term VTE prophylaxis (P=0.01 and P<0.001 respectively).[49]
- Safety and efficacy of dabigatran etexilate for the prevention of DVT and PE after hip replacement surgery was established in two clinical trials, RE-NOVATE and RE-NOVATE II. Dabigatran etexilate 220 mg once daily was compared to enoxaparin 40 mg once daily in a double-blind, double-dummy

design for 28 to 35 days.[50,51] In RE-NOVATE, the absolute difference in dabigatran etexilate when compared to enoxaparin was -0.7% (no P value reported).[50] In RE-NOVATE II, the absolute difference was -1.1% (P=0.43).[51] In both studies, dabigatran etexilate 220 mg once daily was shown to be non-inferior to enoxaparin 40 mg once daily by having an absolute difference in total VTE and all-cause mortality below the pre-established non-inferiority margin of 7.7%.

- Approval of rivaroxaban for use in AF was based on the clinical evidence for safety and efficacy derived from the non inferiority, ROCKET-AF trial (N=14,264). Results demonstrated that rivaroxaban (15 or 20 mg/day) is non inferior to warfarin for the prevention of stroke or systemic embolism (*P*<0.001 for non inferiority), with no increased risk of major bleeding (*P*=0.44). Within ROCKET-AF, intracranial and fatal bleeding were significantly less frequent with rivaroxaban (*P*=0.02).[36]
    - In a subgroup analysis of ROCKET-AF evaluating the efficacy and safety of rivaroxaban among patients with and without previous stroke or transient ischemic attack, it was revealed that the relative efficacy and safety of rivaroxaban compared to warfarin was not different between these two patient populations. Ultimately, results support the use of rivaroxaban as an alternative to warfarin for the prevention of recurrent as well as initial stroke in patients with AF.[37]
- Approval of rivaroxaban for prophylaxis of DVT was based on the clinical evidence for safety and efficacy derived from the global program of clinical trials known collectively as RECORD (1 [N=4,541], 2 [N=2,509], 3 [2,531], and 4 [N=3,148]). All four trials compared rivaroxaban to enoxaparin for thromboprophylaxis in patients undergoing total elective hip and knee replacement surgeries.[53-56]
    - In all four trials, rivaroxaban significantly reduced the risk of the primary composite endpoint of any DVT, nonfatal PE, or death from any cause compared to enoxaparin, with no increased risk of major bleeding, any bleeding, and hemorrhagic wound complications.
- The approval of rivaroxaban for the treatment of DVT and PE, and for the reduction in the risk of recurrence of DVT and PE was based on two open-label, non inferiority trials. In EINSTEIN-DVT, 3,449 patients with an acute, symptomatic, objectively confirmed proximal DVT without symptomatic PE received rivaroxaban 15 mg twice daily for three weeks followed by 20 mg once daily or enoxaparin 1 mg/kg subcutaneously twice daily plus warfarin or acenocoumarol adjusted to maintain an INR of 2.0 to 3.0. The occurrence of symptomatic, recurrent VTE was 2.1% in the rivaroxaban group and 3.0% in the standard therapy group (HR, 0.68; 95% CI, 0.44 to 1.04; *P*<0.001 for non inferiority and *P*=0.08 for superiority).[57]
    - Clinically relevant (first major or clinically relevant non major) bleeding was similar between the treatment groups (*P*=0.77). In a 12-month extension, EINSTEIN-EXT, symptomatic, recurrent VTE occurred in eight patients receiving rivaroxaban and 42 patients receiving placebo (1.3 vs 7.1%; HR, 0.18; 95% CI, 0.09 to 0.39; *P*<0.001).[57]
- In 4,832 patients with an acute, symptomatic PE, with or without symptomatic DVT (EINSTEIN-PE), there was a symptomatic recurrence of VTE in 50 patients treated with rivaroxaban compared to 44 patients treated with standard-therapy (HR, 1.12; 95% CI, 0.75 to 1.68; *P*=0.003 for non inferiority and *P*=0.57 for superiority).[58]
    - There was no difference between the rivaroxaban and standard therapy treatment groups with regard to major or clinically relevant non major bleeding (HR, 0.90; 95% CI, 0.76 to 1.07; *P*=0.23).[58]
- The FDA approval of edoxaban tosylate was based on two phase III, double-blind, multinational, randomized controlled clinical trials.
    - The second trial compared the efficacy and safety of edoxaban tosylate to warfarin in reducing the risk of stroke and systemic embolic events in adult patients with non-valvular AF. The annualized rate for occurrence of a first stroke (ischemic or hemorrhagic) or a systemic embolic event that occurred during treatment or within three days from the last dose taken was 1.50% with warfarin compared with 1.18% with high-dose edoxaban tosylate (HR, 0.79; 97.5% CI, 0.63 to 0.99; P<0.001) and 1.61% with low-dose edoxaban tosylate (HR, 1.07; 97.5% CI, 0.87 to 1.31; P=0.005). major bleeding during treatment was found to be 3.43% with warfarin compared with 2.75% with high-dose edoxaban tosylate (HR, 0.80; 95% CI, 0.71 to 0.91; P<0.001)

and 1.61% with low-dose edoxaban tosylate (HR, 0.47; 95% CI, 0.41 to 0.55; P<0.001).[35]

- The first study evaluated edoxaban tosylate was compared to warfarin in adult patients with acute venous thromboembolism. Results showed that there was a recurrence of venous thromboembolism in 3.2% of the edoxaban tosylate group as compared with 3.5% in the warfarin group (P<0.001). Edoxaban demonstrated superiority compared to warfarin for clinically relevant bleeding (8.5% compared with 10.3% for the warfarin group [P=0.004]). However, both treatment groups were similar in regards to major bleeding (P=0.35).[52]

**Key Points within the Medication Class**

- According to Current Clinical Guidelines:[10-18]
  - Atrial fibrillation:
    - The 2014 American Heart Association, American College of Cardiology, and Heart Rhythm Society guideline recommends warfarin, or either apixaban, rivaroxaban or dabigatran as an alternative to warfarin for non-valvular atrial fibrillation. Patients who already have excellent INR control would likely gain little by switching to the newer agents. They recommend not using the newer agents in end-stage chronic kidney disease or on hemodialysis due to lack of evidence regarding the risk versus benefit. A specific recommendation to avoid the use of dabigatran for patients with a mechanical heart valve is also made.[10]
    - The 2012 American College of Chest Physicians recommends oral anticoagulation in patients at intermediate to high risk of stroke, with dabigatran etexilate mesylate suggested over adjusted-dose vitamin K antagonist therapy.[12]
  - Thromboprophylaxis:
    - The 2012 American College of Chest Physicians guideline recommends dabigatran etexilate mesylate, rivaroxaban, and adjusted-dose vitamin K antagonist therapy, along with low molecular weight heparin, fondaparinux, apixaban, low dose unfractionated heparin, aspirin, and an intermittent pneumatic compression device, for thromboprophylaxis in total hip and knee arthroplasty. Low molecular weight heparin is suggested in preference to other recommended agents for this indication.[12]
    - In general, other current guidelines are in line with the American College of Chest Physicians.
  - Secondary prevention in post-myocardial infarction:[12,13,16]
    - Warfarin is recommended in post-myocardial infarction patients who have an indication for anticoagulation; however, the evidence surrounding its use in these patients is still evolving.
  - A recent Science Advisory for Healthcare Professionals by the American Heart Association and American Stroke Association states that the choice of antithrombotic treatment should be individualized based on risk factors, cost, tolerability, patient preference, potential for drug interactions, and other clinical characteristics, including time in INR therapeutic range (if taking warfarin). Apixaban, dabigatran etexilate mesylate and rivaroxaban are recommended as an alternative to warfarin in patients with atrial fibrillation and at least one additional risk factor for stroke.[18]
- Other Key Facts:
  - Rivaroxaban for use in atrial fibrillation:[4]
    - The approved package labeling for rivaroxaban acknowledges the low percentage of "time in International Normalized Ratio range" for patients randomized to warfarin within the ROCKET-AF trial as compared to other clinical trials, and states that it is unknown how rivaroxaban compares when patients are well controlled on warfarin.
    - Within the ROCKET-AF trial, an increased incidence of adverse clinical events were noted when patients were transitioned off of rivaroxaban to warfarin or to another vitamin K antagonist.

- The prescribing information for apixaban, dabigatran, edoxaban, and rivaroxaban contain a Black Box Warning regarding an increased risk of thromboembolic events following the discontinuation of treatment.[1-4]
- Apixaban has demonstrated a significant reduction in the risk of stroke and systemic embolism, major bleeding and all-cause mortality compared to warfarin in patients with atrial fibrillation.[19]
- Dabigatran etexilate mesylate 150 mg has demonstrated a significant reduction in the risk of stroke and systemic embolism compared to warfarin in patients with atrial fibrillation; the risk of major bleeding and all-cause mortality was similar between treatments.[26]
- Rivaroxaban was non inferior to warfarin with regard to the reduction in the risk of stroke and systemic embolism in patients with atrial fibrillation (per-protocol analysis) with a similar incidence of major bleeding.[36]
- Apixaban, dabigatran and rivaroxaban All three new oral anticoagulants are associated with a significant reduction in intracranial hemorrhage compared to warfarin.[19,26,36]
- Warfarin is available generically.[9]

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