Therapeutic Class Overview
Oral Anticoagulants

Therapeutic Class

- **Overview/Summary:** Apixaban (Eliquis®), dabigatran etexilate mesylate (Pradaxa®), rivaroxaban (Xarelto®) and warfarin (Coumadin®, Jantoven®) are oral anticoagulants that are Food and Drug Administration (FDA)-approved for various cardiovascular indications.[1-4] Specifically, rivaroxaban and warfarin are approved for use as thromboprophylaxis, and all four agents can be used to manage thromboembolic complications associated with atrial fibrillation. In addition, rivaroxaban is approved for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and for the reduction in the risk of recurrence of DVT and PE.[1-4] The specific FDA-approved indications of the oral anticoagulants are outlined in Table 1.[1-4] Warfarin, a vitamin K antagonist, has been the principle oral anticoagulant for more than 60 years and has extensive, well established data demonstrating its safety and efficacy in all FDA-approved indications.[4,5] Apixaban and rivaroxaban are selective factor Xa inhibitors while dabigatran etexilate mesylate is a direct thrombin inhibitor. While the data for apixaban, dabigatran etexilate mesylate 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 and rivaroxaban are not associated with a narrow therapeutic window, numerous drug-drug and -food interactions, or monitoring requirements. It has been stated that due to the lack of surrogate markers to measure the efficacy of anticoagulation with the new oral anticoagulants, clinicians may find it difficult to find an objective way to assess a patient's adherence to therapy, and whether a fixed-dose regimen can be universally applied to all patients. Currently, there is no antidote to reverse bleeding with apixaban, dabigatran etexilate mesylate or rivaroxaban.[6,7] Warfarin does not require a dosage adjustment in patients with renal impairment, while a lower dose of apixaban, dabigatran etexilate mesylate and rivaroxaban (atrial fibrillation only) is recommended.[1-4] 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] Apixaban and dabigatran etexilate mesylate are approved for twice-daily dosing while rivaroxaban and warfarin are dosed once daily.[1-4] Currently, warfarin is the only oral anticoagulant that is available generically.[8]

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®)	Reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation	Tablet: 2.5 mg 5 mg	-
Dabigatran etexilate mesylate (Pradaxa®)	Reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation	Capsule: 75 mg 150 mg	-
Rivaroxaban (Xarelto®)	Prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism in patients undergoing knee or hip replacement surgery; reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation†; treatment of deep vein thrombosis and pulmonary embolism, and for the reduction in the risk of recurrence of deep vein thrombosis and of pulmonary embolism	Tablet: 10 mg 15 mg 20 mg	-
Warfarin (Coumadin®*, Jantoven®*)	Prophylaxis and treatment of the thromboembolic complications associated with atrial fibrillation and/or cardiac valve	Tablet: 1 mg 2 mg	✔

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
	replacement; prophylaxis and treatment of venous thrombosis and its extension, pulmonary embolism; reduce the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization after myocardial infarction	2.5 mg 3 mg 4 mg 5 mg 6 mg 7.5 mg 10 mg	

* Generic available in at least one dosage form and/or strength.
† There is limited data on the relative effectiveness of rivaroxaban and warfarin in reducing the risk of stroke and systemic embolism when warfarin therapy is well controlled.

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.[3,9-19]
- The efficacy of apixaban in patients with nonvalvular atrial fibrillation (AF) was evaluated in the AVERROES and ARISTOTLE trials.[20,21]
- 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.[20]
- 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).[21]
- 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).[22]
    - 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.
- 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).[24]

- 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).[25]
- 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.[26]
- 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.[27-30]
    - 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).
    - 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).[31]
- 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).
    - 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).[32]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - 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.[33]
    - Atrial fibrillation:
        - The 2011 American College of Cardiology Foundation focused update states that dabigatran etexilate mesylate is useful as an alternative to warfarin, and patients

already receiving warfarin with excellent International Normalized Ratio control may have little to gain by switching to dabigatran etexilate mesylate.[34]
        - 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.[35]
        - Neither organization provides guidance as to the role of apixaban or rivaroxaban in the management of atrial fibrillation.[33-36]
    - 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.[35]
        - In general, other current guidelines are in line with the American College of Chest Physicians.
    - Secondary prevention in post-myocardial infarction:[35,38,39]
        - 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.
- Other Key Facts:
    - Rivaroxaban for use in atrial fibrillation:[3]
        - 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 both apixaban and rivaroxaban contain a Black Box Warning regarding an increased risk of thromboembolic events following the discontinuation of treatment.[1,3]
    - 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.[21]
    - 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.[22]
    - 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.[25]
    - All three new oral anticoagulants are associated with a significant reduction in intracranial hemorrhage compared to warfarin.[21,22,25]
    - Warfarin is available generically.[8]

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Oral Anticoagulants

Overview/Summary

Apixaban (Eliquis®) dabigatran etexilate mesylate (Pradaxa®), rivaroxaban (Xarelto®) and warfarin (Coumadin®, Jantoven®) are oral anticoagulants that are Food and Drug Administration (FDA)-approved for the various cardiovascular indications outlined in Table 2.[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.[5-7] Apixaban and rivaroxaban are selective factor Xa inhibitors while dabigatran etexilate mesylate is a direct thrombin inhibitor (DTI). All are novel oral anticoagulants that are approved to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF).[1-3] Rivaroxaban is also indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery, and for the treatment and reduction in the risk of recurrence of DVT and PE.[3]

Warfarin is a vitamin K antagonist (VKA) that works by interfering with the synthesis of vitamin K dependent clotting factors and anticoagulant proteins C and S. Specifically, warfarin inhibits the vitamin K epoxide reductase enzyme complex, resulting in the blockade of the regeneration of vitamin K_1 epoxide.[4-7] Conversely, the new oral anticoagulants target a single enzyme involved in the coagulation cascade. Dabigatran etexilate mesylate is a prodrug that is converted to dabigatran, a potent, competitive inhibitor of thrombin. As a DTI, dabigatran inhibits the conversion of fibrinogen into fibrin; thereby, inhibiting the development of a thrombus. Both free and fibrin-bound thrombin and thrombin-induced platelet aggregation are inhibited by dabigatran etexilate mesylate.[2,6,7] Apixaban and rivaroxaban both selectively inhibit factor Xa, thereby preventing the generation of thrombin and ultimately preventing platelet activation and the formation of fibrin clots.[1,3,6,7] Warfarin is available generically while apixaban, dabigatran etexilate mesylate and rivaroxaban are branded oral anticoagulants.[8]

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.[9-10] Warfarin therapy is associated with several challenges including a slow onset and offset of action, significant and unpredictable inter-individual variability in pharmacologic response, a narrow therapeutic window necessitating frequent monitoring and numerous food and drug interactions. Moreover, maintenance of a therapeutic level of anticoagulation may be difficult for some patients and requires a good understanding of the pharmacokinetic and pharmacodynamic properties of warfarin.[5,11,12] In comparison to warfarin, treatment with apixaban, dabigatran etexilate mesylate or rivaroxaban does not require routine monitoring, but clinicians may discover it difficult to find an objective way to assess a patient's adherence to therapy, and whether a fixed-dose regimen can be universally applied to all patients. Apixaban and dabigatran etexilate mesylate require twice-daily dosing compared to rivaroxaban and warfarin which are administered once daily.[1-4] Warfarin does not require a dosage adjustment in patients with renal impairment, while a lower dose of apixaban, dabigatran etexilate mesylate and rivaroxaban (in AF only) is recommended.[1-4] 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] The overall bleeding risk appears to be comparable overall between apixaban and aspirin. Clinical trials comparing apixaban to warfarin have demonstrated a lower incidence of major intracranial bleeding and major bleeding at other locations with apixaban, with a similar incidence of gastrointestinal bleeding.[1,13] In clinical trials, warfarin was associated with more intracranial bleeding, while dabigatran etexilate mesylate was associated with more gastrointestinal bleeding.[2,14] In the clinical trial that was the basis for FDA-approval of dabigatran etexilate mesylate, the incidence of myocardial infarction (MI) was higher with dabigatran etexilate mesylate compared to warfarin.[14] Whether or not this is a true risk associated with the agent is unclear; however, a subanalysis of the trial did not demonstrate an increase in MI with either dose of dabigatran etexilate mesylate compared to warfarin.[15] In the trial that was the basis for FDA-approval of rivaroxaban for use in AF, there was no difference in major and clinically relevant nonmajor

bleeding between rivaroxaban and warfarin, but like dabigatran etexilate mesylate, rivaroxaban was associated with a lower risk of intracranial bleeding and a higher incidence of gastrointestinal bleeding compared to warfarin. There was no increase in the risk of MI associated with rivaroxaban in this trial.[16] In clinical trials for DVT prophylaxis, rivaroxaban demonstrated a comparable bleeding profile to enoxaparin, a low molecular weight heparin (LMWH) agent; both treatments were associated with similar rates of major bleeding and hemorrhagic wound complications.[17-20] In trials evaluating the use of rivaroxaban for treatment of DVT and PE and for the reduction in the risk of recurrence, there were comparable rates of clinically relevant bleeding between patients receiving rivaroxaban or standard therapy with enoxaparin.[21,22]

The current clinical guidelines support the use of the oral anticoagulants for their respective FDA-approved indications.[9-10,23-33] In 2011, the American College of Cardiology Foundation published a focused update on the management of AF stating that dabigatran etexilate mesylate is useful as an alternative to warfarin, and patients already receiving warfarin with excellent International Normalized Ratio (INR) control may have little to gain by switching to dabigatran etexilate mesylate. Furthermore, selection of patients with AF who could benefit from dabigatran etexilate mesylate over warfarin should consider individual clinical features including the ability to comply with twice-daily dosing, availability of an anticoagulation management program to sustain routine INR monitoring, patient preferences, cost and other factors.[24] Since this focused update from the American College of Cardiology Foundation, the American College of Chest Physicians published updated guidelines in 2012 regarding antithrombotic therapy and prevention of thrombosis. With regards to management of AF, oral anticoagulation is recommended in patients at intermediate to high risk of stroke, with dabigatran etexilate mesylate suggested over adjusted-dose VKA therapy.[23] Neither organization provides guidance as to the role of apixaban or rivaroxaban in the management of AF.[9-10,23,24] A 2012 Science Advisory for Healthcare Professionals by the American Heart Association and American Stroke Association regarding the use of oral anticoagulants 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 all recommended as an alternative to warfarin in patients with AF and at least one additional risk factor for stroke.[33]

Apixaban, dabigatran etexilate mesylate, rivaroxaban, and adjusted-dose VKA therapy are recommended, along with LMWH, fondaparinux, apixaban, low dose unfractionated heparin, aspirin, and an intermittent pneumatic compression device, for thromboprophylaxis in total hip and knee arthroplasty. According to the American College of Chest Physicians, LMWH is suggested in preference to other recommended agents for this indication. For patients who decline or who are uncooperative with injections or intermittent pneumatic compression devices, apixaban or dabigatran etexilate mesylate is recommended over alternative forms of thromboprophylaxis, with rivaroxaban or adjusted-dose VKA therapy recommended if these two therapies are unavailable. Parenteral anticoagulation (LMWH, fondaparinux, or unfractionated heparin) is recommended for a minimum of five days for the treatment of acute DVT or PE, with the addition of early initiation of VKA therapy. The duration of anticoagulation after treatment of an acute event will depend on whether the patient was currently receiving anticoagulation therapy, if the event was provoked or unprovoked and/or caused by surgery or a nonsurgical transient risk factor and if it was the first or second thromboembolic event.[23]

For secondary prevention in post-MI patients, the American College of Cardiology recommends the use of warfarin in aspirin-allergic patients who have an indication for anticoagulation. Depending on whether a patient is allergic to aspirin or a stent is implanted, warfarin may also be appropriate as combination therapy with aspirin or clopidogrel in post-MI patients. The American College of Cardiology recommends that post-MI patients with persistent or paroxysmal AF receive warfarin, and therapy with warfarin is recommended if evidence of a thrombus is present following an MI. For this indication, warfarin therapy may last at least three months or indefinitely, depending on the patient's risk of bleeding. Despite these recommendations, the role of long-term warfarin therapy in post-MI patients remains controversial, and aspirin remains the preferred antithrombotic.[25,26] The American College of Chest Physicians also provides recommendations for the use of warfarin in this indication, particularly for use as triple therapy with low

dose aspirin and clopidogrel in patients with anterior MI and left ventricular thrombus, or at high risk for left ventricular thrombus, who underwent bare-metal or drug-eluting stent placement.[23]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade Name)	Medication Class	Generic Availability
Apixaban (Eliquis®)	Oral anticoagulant	-
Dabigatran etexilate mesylate (Pradaxa®)	Oral anticoagulant	-
Rivaroxaban (Xarelto®)	Oral anticoagulant	-
Warfarin (Coumadin®*, Jantoven®*)	Oral anticoagulant	✔

*Generic available in at least one dosage form or strength.

Indications

Table 2. Food and Drug Administration-Approved Indications[1-4]

Indication	Apixaban	Dabigatran Etexilate Mesylate	Rivaroxaban	Warfarin
Prophylaxis and treatment of the thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement				✔
Prophylaxis and treatment of venous thrombosis and its extension, pulmonary embolism				✔
Prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism in patients undergoing knee or hip replacement surgery			✔	
Reduce the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization after myocardial infarction				✔
Reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation	✔	✔	✔ *	
Treatment of deep vein thrombosis and pulmonary embolism, and for the reduction in the risk of recurrence of deep vein thrombosis and of pulmonary embolism			✔	

*There is limited data on the relative effectiveness of rivaroxaban and warfarin in reducing the risk of stroke and systemic embolism when warfarin therapy is well controlled.

Apixaban and dabigatran etexilate mesylate has been evaluated for the prevention of venous thromboembolism following arthroplasty of the knee and total hip replacement but are not currently Food and Drug Administration-approved for this indication.[10] Rivaroxaban is currently being evaluated for the treatment acute coronary syndromes. [6,7]

Pharmacokinetics

Table 3. Pharmacokinetics[1-4,6,7]

Generic Name	Bioavailability (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Apixaban	50	27	None	12
Dabigatran etexilate mesylate	3 to 7	80*	Dabigatran (major); 1-, 2-, 3-, 4-O-acylglucuronide (all minor)	12 to 17
Rivaroxaban	80 to 100	66	None	5 to 9
Warfarin	≈100	92	Warfarin alcohols	168

*Intravenous administration.

Clinical Trials

The clinical trials demonstrating the safety and efficacy of the oral anticoagulants in their respective Food and Drug Administration (FDA)-approved indications are described in Table 4.[13-22,34-58] As it has been the principle oral anticoagulant for more than 60 years, the evidence demonstrating the safety and efficacy of warfarin in FDA-approved indications is well established. Because of this, only meta-analyses and Cochrane Reviews evaluating warfarin are included within this review.

The efficacy of apixaban in patients with nonvalvular atrial fibrillation (AF) was evaluated in the Apixaban vs Acetylsalicylic Acid to Prevent Strokes (AVERROES) trail and the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial (ARISTOTLE). AVERROES (N=5,599) was a double-blind, multicenter, randomized controlled trial in which patients were randomized to receive apixaban 5 mg twice daily or aspirin 81 to 324 mg once daily. A dose of 2.5 mg twice daily was used in patients with two or more of the following criteria: age ≥80, body weight ≤60 kg or a serum creatinine level ≥1.5 mg/dL. Patients were ≥50 years of age with AF for at least six months or documented by 12-lead electrocardiogram (EGG) plus at least one of the following risk factors: prior stroke or transient ischemic attack (TIA), age ≥75, arterial hypertension, diabetes mellitus, heart failure (New York Heart Association [NYHA] Class ≥2), a left ventricular ejection fraction (LVEF) ≤35% or peripheral artery disease. The incidence of stroke or systemic embolism, the primary endpoint, was significantly lower 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 statistically significant difference in the incidence of major bleeding between the apixaban and aspirin groups (1.4 vs 1.2% per year, respectively; HR, 1.13; 95% CI, 0.74 to 1.75; *P*=0.57). The incidence of intracranial bleeding (0.4 vs 0.4% per year; *P*=0.69), extracranial bleeding (1.1 vs 0.9% per year; *P*=0.42), gastrointestinal bleeding (0.4 vs 0.4% per year; *P*=0.71), nongastrointestinal bleeding (0.6 vs 0.4% per year; *P*=0.22) or fatal bleeding (0.1 vs 0.2% per year; *P*=0.53) was not significantly different between the apixaban and aspirin groups.[34]

In ARISTOTLE (N=18,201), a large, double-blind, multicenter, randomized controlled trial, patients with AF or flutter and at least one additional risk factor for stroke 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). A dose of 2.5 mg twice daily was used in patients with two or more of the following criteria: age ≥80, body weight ≤60 kg or a serum creatinine level ≥1.5 mg/dL. The incidence of stroke or systemic embolism, the primary endpoint, was significantly lower 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). Apixaban treatment was associated with a significantly lower incidence of major intracranial bleeding (0.33 vs 0.80% per year; HR, 0.42; 95% CI, 0.30 to 0.58; *P*<0.001), and major bleeding at other locations (1.79 vs 2.27% per year; HR, 0.79; 95% CI, 0.68 to 0.93; *P*=0.004) compared to warfarin treatment. There was a similar incidence of major gastrointestinal bleeding between treatments (0.76 vs 0.86% per year, respectively; HR, 0.89; 0.70 to 1.15; *P*=0.37). The rate of myocardial infarction (MI) was similar between the apixaban and warfarin groups (0.53 vs 0.61% per year, respectively; HR, 0.88; 95% CI, 0.66 to 1.17; *P*=0.37). Apixaban treatment was associated with a significantly lower incidence of death from any cause (3.52 vs 3.94% per year; HR, 0.89; 95% CI, 0.80 to

0.998; *P*=0.047) compared to warfarin treatment; a benefit that has not been demonstrated with either dabigatran etexilate mesylate or rivaroxaban.[13]

Approval of dabigatran etexilate mesylate for use in AF was based on the clinical evidence for safety and efficacy derived from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial (N=18,113). The RE-LY trial was a non inferiority, multicenter, randomized, parallel-group trial comparing two blinded doses of dabigatran etexilate mesylate (110 and 150 mg twice daily) with open-label warfarin in patients with nonvalvular, persistent, paroxysmal, or permanent AF. Patients enrolled in the RE-LY trial also had at least one of the following risk factors: previous stroke, TIA or systemic embolism; LVEF <40%; symptomatic heart failure, NYHA Class ≥2; age >75 or age ≥65 plus diabetes, coronary artery disease, or hypertension. For the primary composite endpoint, occurrence of stroke and systemic embolism, both doses of dabigatran etexilate mesylate demonstrated non inferiority to warfarin (*P*<0.001). Specifically, the primary endpoint occurred at a rate of 1.53% per year (relative risk [RR], 0.91; 95% CI, 0.74 to 1.11; *P*=0.34) and 1.10% per year (RR, 0.66; 95% CI, 0.53 to 0.82; *P*<0.001) for dabigatran etexilate mesylate 110 and 150 mg compared to 1.69% per year with warfarin. The 150 mg dose of dabigatran etexilate mesylate achieved "superiority" over warfarin; however, the 110 mg dose did not. The treatment effect observed with dabigatran etexilate mesylate was primarily a reduction in the incidence of stroke. The rate of major bleeding (life-threatening, non life-threatening, and gastrointestinal bleeding) was also reduced with dabigatran etexilate mesylate compared to warfarin (dabigatran etexilate mesylate 110 mg: RR, 0.80; 95% CI, 0.69 to 0.93; *P*=0.003; dabigatran etexilate mesylate 150 mg: RR, 0.93; 95% CI, 0.81 to 1.07; *P*=0.31). No significant differences were observed between dabigatran etexilate mesylate and warfarin in regard to the rate of death from any cause and pulmonary embolism (PE). However, the rate of MI was higher (*P*=0.048 with dabigatran etexilate mesylate 150 mg vs warfarin) and the rate of hospitalization was lower (*P*=0.003 with dabigatran etexilate mesylate 110 mg vs warfarin) with dabigatran etexilate mesylate.[14] Several subgroup analyses of the RE-LY trial have been published.[15,39-41] In one analysis, it was revealed that previous exposure to a vitamin K antagonist does not influence the benefits of dabigatran etexilate mesylate compared to warfarin.[39] Another revealed that the effects of dabigatran etexilate mesylate in patients with a previous stroke or TIA are consistent with those of other patients in the RE-LY trial.[40] A 2012 subgroup analysis 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.[15] 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).[58]

In terms of the evidence demonstrating the efficacy of dabigatran etexilate mesylate for the prevention of stroke and systemic embolization in patients with nonvalvular AF, a phase II, randomized controlled trial was conducted to determine whether a dose-related incidence of bleeding was to be expected with the administration of the agent, and to determine what doses should be used in future clinical trials for further evaluation. This 12-week trial established a dose response for bleeding and an upper limit of tolerability (300 mg twice daily plus aspirin) for dabigatran etexilate mesylate based on the frequency of major and clinically significant bleeding events.[47] Of note, the FDA-approved dosing for dabigatran etexilate mesylate in patients with adequate renal function is 150 mg twice-daily.[2]

Approval of rivaroxaban for use in AF was based on results from the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared to Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) in which 14,264 patients with nonvalvular AF who were considered to be at increased risk for stroke were enrolled. Patients received rivaroxaban 20 mg once daily (or 15 mg once daily in patients with renal impairment) or dose-adjusted warfarin (to target an INR of 2.0 to 3.0). The primary endpoint, a composite of stroke or systemic embolism in the per-protocol population, occurred in 188 patients (1.7% per year) with rivaroxaban and 241 patients (2.2% per year) with warfarin (HR, 0.79; 95% CI, 0.66 to 0.96; *P*<0.001 for non inferiority). The results from the intention-to-treat population did not achieve "superiority" (*P*=0.12).[16] Package labeling for rivaroxaban acknowledges the low percentage of

"time in INR range" for patients randomized to warfarin as compared to other clinical trials, and states that is it unknown how rivaroxaban compares to warfarin when patients are well controlled on warfarin.[2] There was no difference in the rate of major and clinically relevant nonmajor bleeding between rivaroxaban and warfarin (14.9 and 14.5% per year, respectively; HR, 1.03; 95% CI, 0.96 to 1.11; *P*=0.44). Rates of intracranial hemorrhage were significantly lower with rivaroxaban (0.5 vs 0.7% per year; HR, 0.67; 95% CI, 0.47 to 0.93; *P*=0.02); however, the rate of major bleeding from a gastrointestinal site was significantly higher with rivaroxaban (3.2 vs 2.2%; *P*<0.001) compared to warfarin.[16] In a subgroup analysis of ROCKET-AF evaluating the efficacy and safety of rivaroxaban among patients with and without previous stroke or TIA, 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.[45]

Approval of rivaroxaban for prophylaxis of DVT was based on the results of the Regulation in Orthopedic Surgery to Prevent Deep Vein thrombosis and Pulmonary Embolism (RECORD) trials. The RECORD program consists of four individual trials (RECORD1, 2, 3 and 4) evaluating the safety and efficacy of rivaroxaban for thromboprophylaxis in patients undergoing total elective hip and knee replacement surgeries. Primary and secondary endpoints were similar among the four trials and major bleeding was defined as bleeding that was fatal, involved a critical organ or required reoperation, clinically overt bleeding outside the surgical site that was associated with a decrease in the hemoglobin level of at least 2 g/dL, or a bleed requiring an infusion of two units or more of blood.[17-20]

RECORD1 (N=4,541) and RECORD2 (N=2,509) were two, double-blind, multicenter, randomized controlled trials evaluating rivaroxaban for thromboprophylaxis in patients undergoing hip replacement surgery. Both trials compared rivaroxaban 10 mg once daily to enoxaparin 40 mg once daily. In RECORD1 rivaroxaban and enoxaparin were both administered for 35 days, while in RECORD2 rivaroxaban was administered for 31 to 39 days (extended thromboprophylaxis) and enoxaparin for 10 to 14 days.[17,18] In RECORD1, the risk of the primary composite endpoint of any DVT, nonfatal PE, or death from any cause up to 36 days was significantly reduced with rivaroxaban compared to enoxaparin (1.1 vs 3.7%; absolute risk reduction [ARR], -2.6%; 95% CI, -3.7 to -1.5; *P*<0.001). Treatment with rivaroxaban also significantly reduced the risk of major VTE (0.2 vs 2.0%; ARR, -1.7%; 95% CI, -2.5 to -1.0; *P*<0.001).[17] Rivaroxaban had no beneficial effect on all-cause mortality (on-treatment: 0.3 vs 0.3%; *P*=1.00, follow-up: 0.1 vs 0.0%; *P*=1.00). The rate of major bleeding was similar between rivaroxaban and enoxaparin (0.3 vs 0.1%; *P*=0.18). In addition, rivaroxaban and enoxaparin had similar rates of any on-treatment bleeding (6.0 vs 5.9%; *P*=0.94) and hemorrhagic wound complications (1.5 vs 1.7%; *P* value were not reported).[17] In RECORD2, rivaroxaban significantly reduced the risk of the primary composite endpoint up to 30 to 42 days (2.0 vs 9.3%; ARR, 7.3%; 95% CI, 5.2 to 9.4; *P*<0.0001). In this trial, the risk of major VTE was significantly reduced with rivaroxaban (0.6 vs 5.1%; ARR, 4.5%; 95% CI, 3.0 to 6.0; *P*<0.0001). Rivaroxaban demonstrated no beneficial effects on all-cause mortality (0.2 vs 0.7%; *P*=0.29). Similar to RECORD1, there were no differences between rivaroxaban and enoxaparin in the rates of major bleeding, any on-treatment nonmajor bleeding, and hemorrhagic wound complications (*P* values not reported).[18]

Rivaroxaban for thromboprophylaxis in patients undergoing knee replacement surgery was evaluated in RECORD3 (N=2,531) and RECORD4 (N=3,148). Both were double-blind, multicenter, randomized controlled trials. The trials compared rivaroxaban 10 mg once daily to either enoxaparin 40 mg once daily (RECORD3) or 30 mg twice daily (RECORD4) for 10 to 14 days. Again, all primary and secondary endpoints were similar to RECORD1 and RECORD2. Furthermore, results from all four trials were consistent.[19,20] In RECORD3, rivaroxaban significantly reduced the risk of the primary composite endpoint compared to enoxaparin up to 17 days (9.6 vs 18.9%; absolute risk difference [ARD], -9.2%; 95% CI, -12.4 to -5.9; *P*<0.001). Rivaroxaban also significantly reduced the rate of major VTE (1.0 vs 2.6%; ARD, -1.6%; 95% CI, -2.8 to -0.4; *P*=0.01) and was not associated with any mortality benefit (*P*=0.21). The rates of major bleeding (*P*=0.77) and any on-treatment bleeding (*P*=0.93) were similar between rivaroxaban and enoxaparin, as well as the rate of hemorrhagic wound complications (*P* value not reported).[15]

RECORD4 demonstrated similar results, except in this trial, there was no difference between rivaroxaban and enoxaparin in the rate of major VTE (*P*=0.1237).[20]

The approval of rivaroxaban for the treatment of DVT and PE, and for the reduction in the risk of recurrence of DVT and of PE was based on the Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Deep Vein Thrombosis (EINSTEIN-DVT) trial and the Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Pulmonary Embolism (EINSTEIN-PE) trial. 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 thereafter or enoxaparin 1 mg/kg subcutaneously (SC) 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 patients receiving rivaroxaban compared to 3.0% of patients receiving standard therapy (HR, 0.68; 95% CI, 0.44 to 1.04; *P*<0.001 for non inferiority and *P*=0.08 for superiority). The occurrence of clinically relevant (first major or clinically relevant nonmajor) bleeding was similar between the treatment groups (HR, 0.97; 95% CI, 0.76 to 1.22; *P*=0.77). In a 12-month extension study, 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).[21] In 4,832 patients with an acute, symptomatic PE with objective confirmation, 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). There was no statistically significant difference between the rivaroxaban and standard therapy treatment groups with regard to major or clinically relevant nonmajor bleeding (HR, 0.90; 95% CI, 0.76 to 1.07; *P*=0.23).[22]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Reducing the Risk of Stroke and Systemic Embolism in Patients with Nonvalvular Atrial Fibrillation				
Connolly et al[34] AVERROES Apixaban 5 mg BID vs aspirin 81 to 324 mg QD An apixaban dose of 2.5 mg BID was used in patients with two or more of the following criteria: age ≥80, body weight ≤60 kg or a serum creatinine level ≥1.5 mg/dL.	AC, DB, MC, PG, RCT Patients ≥50 years of age with AF for at least six months before enrollment or documented by 12-lead ECG on the day of screening and at least one of the following risk factors: prior stroke or TIA, age ≥75, arterial hypertension, diabetes mellitus, heart failure (NYHA Class ≥2), a LVEF ≤35%, or peripheral artery disease Patients could not be receiving VKA therapy because it had already been unsuitable for them or was expected to be unsuitable.	N=5,599 1.1 years	Primary: Incidence of stroke (ischemic or hemorrhagic) or systemic embolism and major bleeding Secondary: Rates of MI, death from vascular causes, death from any cause and composite of major vascular events	Primary: The incidence of stroke or systemic embolism was significantly lower in patients randomized to receive treatment with apixaban compared to treatment with aspirin (1.6 vs 3.7% per year; HR, 0.45; 95% CI, 0.32 to 0.62; *P*<0.001). The incidence of ischemic stroke was significantly lower in the apixaban treatment group (1.1 vs 3.0% per year; HR, 0.37; 95% CI, 0.25 to 0.55; *P*<0.001); however, there was no difference between the groups with regard to hemorrhagic stroke (0.2 vs 0.3% per year, respectively; HR, 0.67; 95% CI, 0.24 to 1.88; *P*=0.45). There was no statistically significant difference in the incidence of major bleeding in the apixaban treatment group compared to the aspirin treatment group (1.4 vs 1.2% per year, respectively; HR, 1.13; 95% CI, 0.74 to 1.75; *P*=0.57). The incidences of intracranial bleeding (0.4 vs 0.4% per year; *P*=0.69), extracranial bleeding (1.1 vs 0.9% per year; *P*=0.42), gastrointestinal bleeding (0.4 vs 0.4% per year; *P*=0.71), nongastrointestinal bleeding (0.6 vs 0.4% per year; *P*=0.22) and fatal bleeding (0.1 vs 0.2% per year; *P*=0.53) were not significantly different between the apixaban and aspirin treatment groups. Secondary: The incidence of MI was similar between the apixaban and aspirin treatment groups (0.8 vs 0.9% per year, respectively; HR, 0.86; 95% CI, 0.50 to 1.48; *P*=0.59). The incidence of death from vascular causes (2.7 vs 3.1% per year, respectively; HR, 0.87; 95% CI, 0.65 to 1.17; *P*=0.37) or death from any cause (3.5 vs 4.4% per year; HR, 0.79; 95% CI, 0.62 to 1.02; *P*=0.07) was not significantly different between patients receiving apixaban or aspirin. The composite rate of stroke, systemic embolism, MI, death from vascular causes or major bleeding was significantly lower in the apixaban group

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				compared to the aspirin group (ITT, 5.3 vs 7.2% per year; HR, 0.74; 95% CI, 0.60 to 0.90; *P*=0.003; on-treatment analysis, 4.0 vs 6.3% per year; HR, 0.64; 95% CI, 0.51 to 0.80; *P*<0.001). Treatment with apixaban significantly reduced the incidence of hospitalization for cardiovascular causes compared to treatment with aspirin (12.6 vs 15.9% per year; HR, 0.79; 95% CI, 0.69 to 0.91; *P*<0.001). The rate of clinically relevant nonmajor bleeding (3.1 vs 2.7% per year; HR, 1.15; 95% CI, 0.86 to 1.54; *P*=0.35) and minor bleeding (6.3 vs 5.0% per year; HR, 1.24; 95% CI, 1.00 to 1.53; *P*=0.50) was similar between the apixaban and aspirin treatment groups.
Diener et al[35] AVERROES Apixaban 5 mg BID vs aspirin 81 to 324 mg QD An apixaban dose of 2.5 mg BID was used in patients with two or more of the following criteria: age ≥80, body weight ≤60 kg or a serum creatinine level ≥1.5 mg/dL.	Subanalysis of AVERROES[34] Patients enrolled in the AVERROES trial stratified based on previous stroke and TIA	N=5,599 1.1 years	Primary: Incidence of stroke (ischemic or hemorrhagic) or systemic embolism and major bleeding Secondary: Rates of MI, death from vascular causes, death from any cause and composites of major vascular events	Primary: The incidence of stroke or systemic embolism was significantly lower in patients with no previous stroke or TIA compared to patients with a history of stroke or TIA (2.36 vs 5.73% per year; HR, 2.38; 95% CI, 1.66 to 3.34; *P*<0.0001). There was a significantly lower incidence of stroke or systemic embolism with apixaban treatment compared to aspirin treatment in those without previous stroke or TIA (HR, 0.51; 95% CI, 0.35 to 0.74) and in those with a previous stroke or TIA (HR; 0.29; 95% CI, 0.15 to 0.60); however, the difference between the groups was not statistically significant (*P*=0.17). The incidence of major bleeding was not significantly different between the apixaban and aspirin treatment groups, regardless of previous stroke or TIA history (*P*=0.73). Secondary: There was no significant difference between apixaban and aspirin treatment with regard to the incidence of MI. Moreover, the difference in MI between patients with a history of stroke or TIA and those without a history of stroke or TIA was not statistically significant (*P*=0.33). There was no significant difference between the apixaban and aspirin treatment groups in the incidence of death from vascular causes, regardless

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				of previous stroke history (*P*=0.79). There was no statistically significant difference between the apixaban and aspirin treatment groups with regard to the incidence of stroke (*P*=0.26), ischemic or unspecified stroke (*P*=0.36), hemorrhagic stroke (*P*=0.25), disabling or fatal stroke (*P*=0.32) or death from any cause (*P*=0.89) between patients with and without a prior history of stroke or TIA. Similarly, no significant differences in intracranial bleeding (*P*=0.92), extracranial or unclassified bleeding (*P*=0.49) or gastrointestinal bleeding (*P*=0.89) were observed between the groups with regard to prior stroke or TIA history.
Flaker et al[36] AVERROES Apixaban 5 mg BID vs aspirin 81 to 324 mg QD An apixaban dose of 2.5 mg BID was used in patients with two or more of the following criteria: age ≥80, body weight ≤60 kg or a serum creatinine level ≥1.5 mg/dL.	Subanalysis of AVERROES[34] Patients enrolled in the AVERROES trial who experienced bleeding during the treatment period	N=5,599 1.1 years	Primary: Major bleeding and clinically relevant nonmajor bleeding Secondary: Not reported	Primary: There were 44 major hemorrhages in the apixaban group and 39 in the aspirin group. There were 96 clinically relevant nonmajor hemorrhages in the apixaban group and 84 in the aspirin group. Three patients in the apixaban group and seven patients in the aspirin group had both severities of bleeding. There was a similar incidence of major bleeding (HR, 1.13; 95% CI, 0.74 to 1.75; *P*=0.57), clinically relevant nonmajor bleeding (HR, 1.15; 95% CI, 0.86 to 1.54; *P*=0.35) and major or clinically relevant nonmajor bleeding (HR, 1.18; 95% CI, 0.92 to 1.51; *P*=0.19) between the apixaban and aspirin treatment groups. Of patients who experienced bleeding during the treatment with apixaban and aspirin, respectively, the incidence of major intracranial bleeding (0.35 vs 0.41% per year; *P*=0.69), gastrointestinal bleeding (0.35 vs 0.45% per year; *P*=0.56), and surgical or trauma bleeding (0.19 vs 0.16% per year; *P*=0.75) was not significantly different between the groups. With regard to major or clinically relevant nonmajor bleeding, there was no statistically significant difference between apixaban and aspirin at any site of bleeding (*P*>0.05 for all). The independent predictors of major and clinically relevant nonmajor

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				bleeding that were significantly different between those treated with apixaban and aspirin were the use of nonstudy aspirin >50% of the time (*P*=0.02 for both treatments) and a history of daily/occasional nosebleeds (*P*=0.02 and *P*=0.01, respectively). There were no significant differences in major and clinically relevant nonmajor bleeding when patients were stratified by age, sex, body mass index, study dose of aspirin, or estimated glomerular filtration rate (*P* values not reported). Secondary: Not reported
Granger et al[13] ARISTOTLE Apixaban 5 mg BID vs warfarin 2 mg; dose adjusted to maintain an INR of 2.0 to 3.0 An apixaban dose of 2.5 mg BID was used in patients with two or more of the following criteria: age ≥80, body weight ≤60 kg or a serum creatinine level ≥1.5 mg/dL.	AC, DB, DD, MC, NI, RCT Patients with AF or flutter at baseline or two or more episodes of AF or flutter, as documented by ECG at least two weeks apart in the 12 months before enrollment and at least one of the following risk factors for stroke age ≥75, previous stroke, TIA, systemic embolism, symptomatic heart failure within previous three months or LVEF ≤40% and	N=18,201 1.8 years	Primary: Incidence of stroke (ischemic, hemorrhagic or uncertain type) or systemic embolism and major bleeding Secondary: Death from any cause, rate of MI, composite of stroke, systemic embolism or death from any cause, composite of stroke, systemic embolism, MI or death from any cause, composite of PE or DVT, major bleeding or clinically relevant nonmajor bleeding, any bleeding and adverse events	Primary: Stroke or systemic embolism occurred in 212 patients treated with apixaban and 265 patients treated with warfarin (1.27 vs 1.60% per year, respectively; 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 significantly lowered the incidence of hemorrhagic stroke compared to treatment with warfarin (0.24 vs 0.47% per year; HR, 0.51; 95% CI, 0.35 to 0.75; *P*<0.001). There was no statistically significant difference between the apixaban and warfarin treatment groups with regard to a reduction in ischemic or uncertain type of stroke (0.97 vs 1.05% per year, respectively; HR, 0.92; 95% CI, 0.74 to 1.13; *P*=0.42) or systemic embolism (0.09 vs 0.10% per year, respectively; HR, 0.87; 95% CI, 0.44 to 1.75; *P*=0.70). There was a significantly lower incidence of major bleeding associated with apixaban treatment compared to warfarin treatment (2.13 vs 3.09% per year; HR, 0.69; 95% CI, 0.60 to 0.80; *P*<0.001). Apixaban treatment was associated with a significantly lower incidence of major intracranial bleeding (0.33 vs 0.80% per year; HR, 0.42; 95% CI, 0.30 to 0.58; *P*<0.001), and major bleeding at other locations (1.79 vs 2.27% per year; HR, 0.79; 95% CI, 0.68 to 0.93; *P*=0.004) compared to warfarin treatment. There was a similar incidence of major gastrointestinal bleeding

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	diabetes mellitus or hypertension requiring treatment			between the treatment groups (0.76 vs 0.86% per year, respectively; HR, 0.89; 0.70 to 1.15; *P*=0.37). Secondary: Patients randomized to receive apixaban had a lower incidence of death from any cause (3.52 vs 3.94% per year; HR, 0.89; 95% CI, 0.80 to 0.998; *P*=0.047) compared to patients randomized to warfarin treatment. There was a similar rate of MI between the apixaban and warfarin treatment groups with regard to incidence of MI (0.53 vs 0.61% per year, respectively; HR, 0.88; 95% CI, 0.66 to 1.17; *P*=0.37). The composite of stroke, systemic embolism, or death from any cause was significantly lower in the apixaban treatment group compared to the warfarin treatment group (4.49 vs 5.04% per year; HR, 0.89; 95% CI, 0.81 to 0.98; *P*=0.02). Similarly, the composite of stroke, systemic embolism, MI or death from any cause was significantly lower in the apixaban treatment group compared to the warfarin treatment group (4.85 vs 5.49% per year; HR, 0.88; 95% CI, 0.80 to 0.97; *P*=0.01). The incidence of PE or DVT was similar between the apixaban and warfarin treatment groups (0.04 vs 0.05% per year, respectively; HR, 0.78; 95% CI, 0.29 to 2.10; *P*=0.63). Apixaban treatment was associated with a significantly lower rate of major or clinically relevant nonmajor bleeding compared to warfarin treatment (4.07 vs 6.01% per year; HR, 0.68; 95% CI, 0.61 to 0.75; *P*<0.001). Moreover, apixaban reduced GUSTO severe bleeding, GUSTO moderate or severe bleeding, TIMI major bleeding and TIMI major or minor bleeding compared to warfarin (*P*<0.001 for all). There was a statistically significant reduction in any bleeding in the apixaban treatment group compared to the warfarin treatment group (18.1 vs 25.8% per year; HR, 0.71; 95% CI, 0.68 to 0.75; *P*<0.001).

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				Adverse events occurred in a similar proportion of patients in the apixaban group and in the warfarin group (81.5 and 83.1%, respectively) as did the proportion of patients who experienced serious adverse events (35.0 and 36.5%, respectively). The rates of liver function abnormalities were similar between the treatment groups.
Easton et al[37] ARISTOTLE Apixaban 5 mg BID vs warfarin 2 mg; dose adjusted to maintain an INR of 2.0 to 3.0 An apixaban dose of 2.5 mg BID was used in patients with two or more of the following criteria: age ≥80, body weight ≤60 kg or a serum creatinine level ≥1.5 mg/dL.	Subanalysis of ARISTOTLE[13] Patients enrolled in the ARISTOTLE trial stratified based on previous stroke and TIA	N=18,201 1.8 years	Primary: Incidence of stroke (ischemic, hemorrhagic or uncertain type) or systemic embolism and major bleeding Secondary: Death from any cause, incidence of stroke, hemorrhagic stroke, ischemic or uncertain type of stroke, disabling or fatal stroke, cardiovascular death, intracranial, gastrointestinal and total bleeding	Primary: The relative reduction in the risk of stroke or systemic embolism with apixaban compared to warfarin was not significantly different among patients with a history of previous stroke (HR, 0.76; 95% CI, 0.56 to 1.03) and those without (HR, 0.82; 95% CI, 0.65 to 1.03) a previous history of stroke or TIA (*P*=0.71). Treatment with apixaban significantly reduced the risk of major bleeding compared to warfarin in patients with a history of stroke or TIA (HR, 0.73; 95% CI, 0.55 to 0.98) and patients without a history of stroke or TIA (HR, 0.68; 95% CI, 0.58 to 0.80); however, the difference between the groups was not statistically significant (*P*=0.69). Secondary: The reduction in death from any cause with apixaban vs warfarin was similar among patients with a history of stroke or TIA (HR, 0.0.89; 95% CI, 0.70 to 1.12) and patients without a stroke or TIA history (HR, 0.90; 95% CI, 0.79 to 1.02; *P*=0.89). The reduction in the risk of stroke was not significantly different between those with a prior history of stroke or TIA (HR, 0.71; 95% CI, 0.52 to 0.98) and those without a history of stroke or TIA (HR, 0.84; 95% CI, 0.67 to 1.06) who were treated apixaban compared to warfarin (*P*=0.40). The reduction in the risk of hemorrhagic stroke with apixaban compared to warfarin was similar among patients with a history of stroke or TIA (HR, 0.40; 95% CI, 0.21 to 0.78) and patients without a history of stroke or TIA (HR, 0.59; 95% CI, 0.37 to 0.94; *P*=0.35). There was no statistically significant difference in the reduction in ischemic

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				or unknown type of stroke with apixaban compared to warfarin among patients with a history of stroke or TIA (HR, 0.86; 95% CI, 0.60 to 1.22) and patients without a stroke or TIA history (HR, 0.97; 95% CI, 0.74 to 1.26; *P*=0.61). The reduction in disabling or fatal stroke with apixaban compared to warfarin was similar among patients with a history of stroke or TIA (HR, 0.87; 95% CI, 0.57 to 1.34) and patients without a stroke or TIA history (HR, 0.60; 95% CI, 0.41 to 0.86; *P*=0.18). The significant reduction in death from any cause with apixaban compared to warfarin was consistent among patients with a history of stroke or TIA (HR, 0.73; 95% CI, 0.55 to 0.98) and patients without a stroke or TIA history (HR, 0.68; 95% CI, 0.58 to 0.80; *P*=0.69). There was no significant reduction in the risk of total bleeding (*P*=0.70), intracranial bleeding (*P*=0.60) or gastrointestinal bleeding (*P*=0.87) between patients with a previous history of stroke or TIA who received apixaban compared to warfarin and patients without a history of stroke or TIA.
Lopes et al[38] ARISTOTLE Apixaban 5 mg BID vs warfarin 2 mg; dose adjusted to maintain an INR of 2.0 to 3.0 An apixaban dose of 2.5 mg BID was used in patients with two or more of the following criteria: age ≥80, body weight ≤60 kg or a	Subanalysis of ARISTOTLE[13] Patients enrolled in the ARISTOTLE trial stratified based on $CHADS_2$, CHA_2D_S2VASc and HAS-BLED scores	N=18,201 1.8 years	Primary: Incidence of stroke (ischemic, hemorrhagic or uncertain type) or systemic embolism and major bleeding Secondary: MI, death from any cause, intracranial bleeding, TIMI major or minor bleeding, GUSTO moderate or severe bleeding, any bleeding and net clinical events (stroke	Primary: Apixaban significantly reduced stroke or systemic embolism with no evidence of a differential effect by risk of stroke ($CHADS_2$ score; *P*=0.4457, CHA_2DS_2VASc score *P*=0.1210) or bleeding (HAS-BLED score *P*=0.9422). Patients treated with apixaban experienced lower rates of major bleeding compared to patients treated with warfarin, with no difference between score categories ($CHADS_2$; *P*=0.4018, CHA_2DS_2VASc; *P*=0.2059 and HAS-BLED; *P*=0.7127). Secondary: Patients treated with apixaban had significantly lower rates of stroke or systemic embolism (*P*=0.0114), mortality (*P*=0.0465), major bleeding (*P*<0.0001), intracranial bleeding (*P*<0.0001), and any bleeding (*P*<0.0001) compared to patients receiving warfarin, regardless of $CHADS_2$ score. The benefits of apixaban compared to warfarin for all endpoints across CHA_2DS_2VASc categories were similar to those seen across $CHADS_2$ score

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serum creatinine level ≥1.5 mg/dL.			or systemic embolism, major bleeding and all-cause mortality)	categories. There was no difference in the rate of MI between patients in different risk categories. Regardless of HAS-BLED score, patients receiving treatment with apixaban had lower rates of stroke or systemic embolism (*P*=0.0114), mortality (*P*=0.0465), major bleeding (*P*<0.0001), TIMI major or minor bleeding (*P*<0.0001), GUSTO severe or moderate bleeding (P<0.0001), and any bleeding (*P*<0.0001) compared to patients treated with warfarin. The reduction in intracranial bleeding with apixaban compared to warfarin was greater in patients with a HAS-BLED score of three or higher (HR, 0.22; 95% CI, 0.10 to 0.48) compared to patients with a HAS-BLED score of less than one (HR, 0.66; 95% CI, 0.39 to 1.12); however, the difference was not significant (*P*=0.0604). Irrespective of $CHADS_2$, CHA_2DS_2VASc, and HAS-BLED score, patients randomized to receive treatment with apixaban experienced lower rates of the composite of stroke, systemic embolism, major bleeding, and all-cause mortality compared to patients randomized to warfarin. These results were driven mainly by reductions in bleeding.
Connolly et al[14] RE-LY Dabigatran 110 mg BID vs dabigatran 150 mg BID vs warfarin 1, 3, or 5 mg; dose adjusted to maintain an INR of 2.0 to 3.0 (OL)	DB, MC, RCT Patients with AF documented on ECG performed at screening or within six months of enrollment and at least one of the following: previous stroke or TIA, LVEF <40%, heart failure (NYHA Class ≥2) symptoms within six months before screening and ≥75	N=18,113 2 years	Primary: Composite of stroke or systemic embolism, major hemorrhage Secondary: Death, MI, PE, TIA, hospitalization	Primary: Both doses of dabigatran were non inferior to warfarin (*P*<0.001). Stroke or systemic embolism occurred in 182 dabigatran 110 mg- (1.53% per year), 134 dabigatran 150 mg (-1.1% per year) and 199 warfarin-treated patients (1.69% per year). The 150 mg dose of dabigatran was “superior” to warfarin (RR, 0.66; 95% CI, 0.53 to 0.82; *P*<0.001), but the 110 mg dose was not (RR, 0.91; 95% CI, 0.74 to 1.11; *P*=0.34). Rates of hemorrhagic stroke were 0.38, 0.12 (RR, 0.31; 95% CI, 0.17 to 0.56; *P*<0.001) and 0.10% (RR, 0.26; 95% CI, 0.14 to 0.49; *P*<0.001) per year in warfarin-, dabigatran 110 mg- and dabigatran 150 mg-treated patients. The rate of major bleeding (life-threatening, non life-threatening and gastrointestinal) was 3.36, 2.71 (RR, 0.80; 95% CI, 0.69 to 0.93; *P*=0.003) and 3.11% (RR, 0.93; 95% CI, 0.81 to 1.07; *P*=0.31) per year in warfarin-, dabigatran 110 mg- and dabigatran 150 mg-treated patients. Rates of life-

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	years of age or 65 to 74 years of age plus diabetes, hypertension or CAD			threatening bleeding, intracranial bleeding and major or minor bleeding were higher in warfarin-treated patients (1.80, 0.74 and 18.15%, respectively) compared to either dabigatran 110 (1.22, 0.23 and 14.62%, respectively) or 150 mg-treated patients (1.45, 0.30 and 16.42%, respectively) (*P*<0.05 for all comparisons of dabigatran and warfarin). There was a significantly higher rate of major gastrointestinal bleeding in dabigatran 150 mg-treated patients compared to warfarin-treated patients (*P*=0.43 for dabigatran 110 mg vs warfarin and *P*<0.001 for dabigatran 150 mg vs warfarin). The net clinical benefit outcome consisted of major vascular events, major bleeding and death. The rates of this combined outcome were 7.64, 7.09 (RR, 0.92; 95% CI, 0.84 to 1.02; *P*=0.10) and 6.91% (RR, 0.91; 95% CI, 0.82 to 1.00; *P*=0.04) per year in warfarin, dabigatran 110 mg- and dabigatran 150 mg-treated patients. Secondary: Rates of death from any cause were 4.13, 3.75 (RR, 0.91; 95% CI, 0.80 to 1.03; *P*=0.13) and 3.64% (RR, 0.88; 95% CI, 0.77 to 1.00; *P*=0.051) per year in warfarin-, dabigatran 110 mg- and dabigatran 150 mg-treated patients. The rate of MI was 0.53, 0.72 (RR, 1.35; 95% CI, 0.98 to 1.87; *P*=0.07) and 0.74% (RR, 1.38; 95%, 1.00 to 1.91; *P*=0.048) per year in warfarin-, dabigatran 110 mg- and dabigatran 150 mg-treated patients. The rate of PE was 0.09, 0.12 (RR, 1.26; 95% CI, 0.57 to 2.78; *P*=0.56) and 0.15% (RR, 1.61; 95% CI, 0.76 to 3.42; *P*=0.21) per year in warfarin-, dabigatran 110 mg- and dabigatran 150 mg-treated patients. Data regarding the incidences of TIA were not reported. The rate of hospitalization was 20.8, 19.4 (RR, 0.92; 95% CI, 0.87 to 0.97; *P*=0.003) and 20.2% (RR, 0.97; 95% CI, 0.92 to 1.03; *P*=0.34) per year in warfarin-, dabigatran 110 mg- and dabigatran 150 mg-treated patients.
Ezekowitz et al[39] RE-LY	Subanalysis of RE-LY[14]	N=18,113 2 years	Primary: Composite of stroke or systemic embolism,	Primary: Approximately half of the patients were VKA-naïve (50.4%).

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Dabigatran 110 mg BID vs dabigatran 150 mg BID vs warfarin 1, 3, or 5 mg; dose adjusted to maintain an INR of 2.0 to 3.0 (OL)	Patients enrolled in the RE-LY trial who were naïve to and experienced with VKAs		major hemorrhage Secondary: Death, MI, PE, TIA, hospitalization	Combined stroke and systemic embolism rates were similar in dabigatran 110 mg-treated patients for both the VKA-naïve and -experienced cohorts compared to warfarin-treated patients (RR, 0.93; 95% CI, 0.70 to 1.25; *P*=0.65 and RR, 0.87; 95% CI, 0.66 to 1.15; *P*=0.32). In dabigatran 150 mg-treated patients, both VKA-naïve (RR, 0.63; 95% CI, 0.46 to 0.87; *P*=0.005) and -experienced cohorts (RR, 0.66; 95% CI, 0.49 to 0.89; *P*=0.007) had significantly lower risk of stroke or systemic embolism compared to warfarin-treated patients. Major bleeding rates were lower in the VKA-experienced cohort in dabigatran 110 mg-treated patients compared to warfarin-treated patients (RR, 0.74; 95% CI, 0.60 to 0.90; *P*=0.003). The VKA-naïve cohort in dabigatran 110 mg-treated patients (RR, 0.87; 95% CI, 0.72 to 1.07; *P*=0.19) and the VKA-naïve (RR, 0.94; 95% CI, 0.77 to 1.15; *P*=0.55) and –experienced cohort (RR, 0.92; 95% CI, 0.76 to 1.12; *P*=0.41) in dabigatran 150 mg-treated patients were similar compared to warfarin-treated patients. Intracranial bleeding events were lower in dabigatran 110 VKA-naïve and -experienced cohorts (RR, 0.27; 95% CI, 0.14 to 0.52; *P*<0.001; RR, 0.32; 95% CI, 0.18 to 0.56; *P*<0.001) and in dabigatran 150 mg VKA-naïve and -experienced cohorts (RR, 0.46; 95% CI, 0.27 to 0.78; *P*=0.005; RR, 0.40; 95% CI, 0.24 to 0.67; *P*<0.001) compared to warfarin-treated patients. Secondary: Rates of life threatening bleeding, disabling stroke and death (when combined) were significantly lower in the VKA-experienced patients in both dabigatran 110 mg- (RR, 0.82; 95% CI, 0.70 to 0.96; *P*=0.01) and 150 mg-treated cohort (RR, 0.80; 95% CI, 0.68 to 0.93; *P*=0.004) compared to warfarin-treated patients, but similar for the VKA-naïve cohort. When comparing this combined outcome in VKA-naïve and -experienced cohorts within treatments, the rate was lower in VKA-experienced cohort than in the -naïve cohort (RR, 0.83; 95% CI, 0.71 to 0.98; *P*=0.03), as was the cardiovascular death rate (RR, 0.73; 95% CI, 0.58 to 0.92; *P*=0.007). In dabigatran 150 mg-treated patients, the rate of this combined outcome trended lower in VKA-experienced cohort. There were no differences in the rates of MI among the treatments.

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				Gastrointestinal bleeding rates were similar for dabigatran 110 mg- and warfarin-treated patients, but significantly higher in both dabigatran 150 mg VKA-naïve (RR, 1.56; 95% CI, 1.15 to 2.10; *P*=0.004) and -experienced cohorts (RR, 1.42; 95% CI, 1.06 to 1.89; *P*=0.02) compared to warfarin-treated patients.
Diener et al (abstract)[40] RE-LY Dabigatran 110 mg BID vs dabigatran 150 mg BID vs warfarin 1, 3, or 5 mg; dose adjusted to maintain an INR of 2.0 to 3.0 (OL)	Subanalysis of RE-LY[14] Patients enrolled in the RE-LY trial who had a previous stroke or TIA	N=18,113 2 years	Primary: Composite of stroke or systemic embolism, major hemorrhage Secondary: Death, MI, PE, TIA, hospitalization	Primary: Within the subgroup of patients with previous stroke or TIA, 1,195, 1,233 and 1,195 patients were from the dabigatran 110 mg, dabigatran 150 mg and warfarin groups. Stroke or systemic embolism occurred in 65 warfarin-treated patients (2.78% per year) compared to 55 (2.32% per year) dabigatran 110 mg- (RR, 0.84; 95% CI, 0.58 to 1.20) and 51 (2.07% per year) dabigatran 150 mg-treated patients (RR, 0.75; 95% CI, 0.52 to 1.08). The rate of major bleeding was significantly lower in dabigatran 110 mg-treated patients (RR, 0.66; 95% CI, 0.48 to 0.90), and similar in dabigatran 150 mg-treated patients (RR, 1.01; 95% CI, 0.77 to 1.34) compared to warfarin-treated patients. Secondary: The effects of both doses of dabigatran compared to warfarin were not different between patients with previous stroke or TIA and those without for any of the outcomes from RE-LY apart from vascular death (dabigatran 110 mg vs warfarin; *P*=0.038).
Wallentin et al[41] RE-LY Dabigatran 110 mg BID vs dabigatran 150 mg BID vs warfarin 1, 3, or 5 mg;	Subanalysis of RE-LY[14] Patients enrolled in the RE-LY trial across the three treatment groups within four groups defined by quartiles of cTTR (<57.1, 57.1 to 65.5, 65.5 to 72.6 and	N=18,113 2 years	Primary: Composite of stroke or systemic embolism, major hemorrhage Secondary: Death, MI, PE, TIA, hospitalization	Primary: In the total population, the rate of the primary outcome of stroke and systemic embolism was reduced from 1.71% per year in warfarin-treated patients, to 1.54% per year in dabigatran 110 mg-treated patients (non inferiority; *P*<0.001) and to 11.1% per year in dabigatran 150 mg-treated patients ("superiority"; *P*<0.001). Event rates seemed to decrease with higher cTTR in warfarin-treated patients; however, there were no significant interactions between cTTR and stroke and systemic embolism in dabigatran- vs warfarin-treated patients. The rate of nonhemorrhagic stroke and systemic embolism seemed to be lower with higher cTTR in warfarin-treated patients (*P*=0.08).

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dose adjusted to maintain an INR of 2.0 to 3.0 (OL) The cTTR was estimated by averaging the TTR for individual warfarin-treated patients.	>72.6%)			In the total population, the rate of major bleeding was 3.57% per year in warfarin-treated patients compared to 2.87 ("superiority"; *P*=0.003) and 3.32% ("superiority"; *P*=0.31) per year in dabigatran 110 mg- and dabigatran 150 mg-treated patients. The rate of major bleeding, as well as major gastrointestinal bleeding, was numerically lower at higher cTTR quartiles in warfarin-treated patients. When comparing major bleedings between dabigatran 150 mg- and warfarin-treated patients, there were benefits at lower cTTR but similar results at higher cTTR (*P*=0.03). The rates of intracranial bleeding in warfarin-treated patients were associated with the cTTR and were consistently lower in dabigatran-treated patients than warfarin-treated patients irrespective of cTTR. There was a higher rate of major gastrointestinal bleeding in dabigatran 150 mg-treated patients compared to warfarin-treated patients at higher cTTR (*P*=0.019). There was an increase in total bleeding rate with increasing cTTR with all three treatments, without any significant interactions between them. Secondary: Mortality rates were 4.13, 3.75 ("superiority"; *P*<0.13) and 3.64% ("superiority"; *P*<0.051) per year in warfarin-, dabigatran 110 mg- and dabigatran 150 mg-treated patients. Total mortality was lower at higher cTTR in warfarin-treated patients; the interaction *P* value was 0.052 for the interaction between cTTR and the effects of dabigatran 110 mg and 0.066 for the effects of dabigatran 150 mg, with differences in mortality at lower cTTR but similar rates at higher cTTR. For all cardiovascular events, including total mortality and major bleeding, there were significantly lower event rates at higher cTTR in warfarin-treated patients. There was a significant interaction between cTTR and the composite of all cardiovascular events when comparing dabigatran 150 mg- and warfarin-treated patients (*P*=0.0006), and dabigatran 110 mg- and warfarin-treated patients (*P*=0.036). These interactions were mainly attributable to significant differences between treatments in the rates of nonhemorrhagic events (*P*=0.017 for dabigatran 110 mg vs warfarin and *P*=0.0046 for dabigatran 150 mg vs warfarin), with advantages at lower cTTR, whereas rates were greater at higher cTTR.

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Hohnloser et al[15] Dabigatran 110 mg BID vs dabigatran 150 mg BID vs warfarin 1, 3, or 5 mg; dose adjusted to maintain an INR of 2.0 to 3.0 (OL)	Subanalysis of RE-LY[14] Patients with AF documented on ECG performed at screening or within six months of enrolment and at least one of the following: previous stroke or TIA, LVEF<40%, heart failure (NYHA Class ≥2) symptoms within six months before screening and ≥75 years of age or 65 to 74 years of age plus diabetes, hypertension or CAD	N=18,113 2 years	Primary: Myocardial and ischemic events Secondary: Not reported	Primary: The annual rates of MI with dabigatran 110 and 150 mg were 0.82 (HR, 1.29; 95% CI, 0.96 to 1.75; *P*=0.09) and 0.81% per year (HR, 1.27; 95% CI, 0.94 to 1.71; *P*=0.12) compared to 0.64% per year with warfarin. When both doses of dabigatran were compared to warfarin results were similar to those obtained when the two doses were compared separately. With regards to the composite outcome of MI, unstable angina, cardiac arrest, and cardiac death, annual rates were 3.16 (HR, 0.93; 95% CI, 0.80 to 1.06; *P*=0.28) and 33.3% per year (HR, 0.98; 95% CI, 0.85 to 1.12; *P*=0.77) with dabigatran 110 and 150 mg compared to 3.41% per year with warfarin. When revascularization events were included, again no significant differences emerged among the three treatments. With regards to the composite outcome of MI, unstable angina, cardiac arrest, cardiac death, revascularization events, and stroke and systemic embolic events, annual rates were 4.76 (HR, 0.93; 95% CI, 0.83 to 1.05; *P*=0.24) and 4.47% per year (HR, 0.88; 95% CI, 0.78 to 0.98; *P*=0.03) with dabigatran 110 and 150 mg compared to 5.10% per year with warfarin. Events prespecified in the net clinical benefit analysis occurred at annual rates of 7.34 (HR, 0.92; 95% CI, 0.84 to 1.01; *P*=0.09) and 7.11% per year (HR, 0.90; 95% CI, 0.82 to 0.99; *P*=0.02) with dabigatran 110 and 150 mg compared to 7.91% per year with warfarin. Patients who had at least one myocardial ischemic event were older and had more coronary risk factors compared to the remainder of the population. Across all treatments, these patients received more antiplatelet medications, β-blockers, and statins at baseline, and they also more often had a $CHADS_2$ score >2. Fifty-six of 87 clinical MIs with dabigatran 110 mg, 59/89 with dabigatran 150 mg, and 46/66 with warfarin occurred on the study drug treatment. MIs that occurred greater than six days after study drug discontinuation were observed in 17, 20, and 12 patients in all three treatment groups. Accordingly, 33, 34, and 30% of all clinical MIs were diagnosed when

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				patients were not taking the study drug in the respective treatment arms. There were 1,886 (31%) CAD/MI patients receiving dabigatran 110 mg, 1,915 (31%) receiving dabigatran 150 mg, and 1,849 (31%) receiving warfarin. The effects of dabigatran compared to warfarin were highly consistent between patients with prior CAD/MI compared to those without. Secondary: Not reported
Hart et al[42] Dabigatran 110 mg BID vs dabigatran 150 mg BID vs warfarin 1, 3, or 5 mg; dose adjusted to maintain an INR of 2.0 to 3.0 (OL)	Subanalysis of RE-LY[14] Patients enrolled in the RE-LY trial who experienced an intracranial hemorrhage while on treatment	N=18,113 2 years	Primary: Intracranial hemorrhages occurring during anticoagulation, including sites, rates, risk factors, associated trauma and outcomes Secondary: Not reported	Primary: There were 154 intracranial hemorrhages, with an overall 30-day mortality of 36%. Intracranial hemorrhages included intracerebral hemorrhages (46%, with 49% mortality), subdural hematomas (45%, with 24% mortality) and subarachnoid hemorrhages (8%, with 31% mortality). Patients with an intracranial hemorrhage were older (P<0.001), had a history of stroke or TIA (P=0.001), more often took aspirin during follow-up (P=0.001), had lower incidence of heart failure (P=0.02) lower estimated creatinine clearances (P<0.001) compared to patients without intracranial hemorrhage. The rate of intracranial hemorrhage was higher with warfarin treatment (0.76% per year) compared to patients receiving dabigatran 150 mg (0.31% per year, RR, 0.40; 95% CI, 0.27 to 0.59) and dabigatran 110 mg (0.23% per year, RR, 0.30; 95% CI, 0.19 to 0.45). Intracranial hemorrhage-related mortality was similar between the treatments. Age was predictive of intracranial hemorrhage among patients treated with dabigatran (RR, 1.06 per year; P=0.002). The independent predictors of developing spontaneous intracerebral bleeding were the assignment to warfarin (RR, 4.1; P<0.001), previous stroke or TIA (RR, 2.7; P<0.001), aspirin use (RR, 1.8; P=0.02) and age (1.04 per year; P=0.02). The rate of spontaneous intracerebral hemorrhage was significantly higher among those assigned to warfarin (0.36% per year) compared to 0.09% per

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				year with dabigatran 150 mg (RR, 0.26; 95% CI, 0.13 to 0.50) and 0.08% with dabigatran 110 mg (RR, 0.23; 95% CI, 0.12 to 0.47). There was no significant difference in mortality associated with spontaneous intracerebral hemorrhage between treatments. Patients with spontaneous intracerebral bleeding in the basal ganglia/thalamus were, on average, younger (*P*=0.04) and more likely to have diabetes (*P*=0.02) compared to those with lobar bleeding. The rate of subdural hematoma was 0.31% per year in the warfarin group compared to 0.20% per year in the dabigatran 150 mg group (RR, 0.65; *P*=0.10) and 0.08% per year in the dabigatran 110 mg group (RR, 0.27; *P*<0.001). The rate of subdural hematomas was significantly higher with dabigatran 150 mg compared to the 110 mg dosage (RR, 2.4; *P*=0.02). Fatal subdural bleeding occurred in 10 patients receiving warfarin compared to five and two patients receiving dabigatran 150 mg and 110 mg, respectively (*P*<0.05 the 110 mg group). Secondary: Not reported
Healey et al[43] Dabigatran 110 mg BID vs dabigatran 150 mg BID vs warfarin 1, 3, or 5 mg; dose adjusted to maintain an INR of 2.0 to 3.0 (OL)	Subanalysis of RE-LY[14] Patients enrolled in the RE-LY trial who required surgery, dental procedures, cardiac catheterization, or invasive diagnostic procedures (including percutaneous biopsy, peripheral angiography, and similar procedures)	N=4,591 2 years	Primary: Perioperative major bleeding, fatal bleeding, bleeding requiring surgery and thrombotic events Secondary: Not reported	Primary: The incidence of perioperative major bleeding was not significantly different between patients receiving dabigatran 110 mg (3.8%) or dabigatran 150 mg (5.1%) compared to patients receiving warfarin (4.6%; *P*>0.05 for both). Perioperative fatal bleeding was similar in the dabigatran 110 mg (RR, 1.57; 95% CI, 0.26 to 9.39; *P*=0.62) or 150 mg treatment groups (RR, 1.01; 95% CI, 0.14 to 7.15; *P*=0.99) compared to the warfarin group. Bleeding requiring surgery was not significantly different in the dabigatran 110 mg (RR, 0.59; 95% CI, 0.26 to 1.33; *P*=0.20) or 150 mg treatment groups (RR, 1.39; 95% CI, 0.73 to 2.63; *P*=0.32) compared to the warfarin group. The incidences cardiovascular death, stroke (all-cause), ischemic stroke, hemorrhagic stroke, systemic embolism, MI, or PE, were low and not significantly different between patients receiving dabigatran 110 mg, 150 mg

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				or warfarin (*P*>0.05 for all). Secondary: Not reported
Ezekowitz et al[44] Dabigatran 50, 150, and 300 mg BID vs warfarin, dose adjusted to maintain an INR of 2.0 to 3.0 (OL) The three doses of dabigatran were combined in a 3x3 factorial fashion with no aspirin or 81 to 325 mg of aspirin QD.	AC, DB, MC, RCT Patients with documented AF with CAD and at least one of the following: hypertension requiring medical treatment, diabetes, symptomatic heart failure (LVEF <40%), previous stroke or TIA or age >75	N=502 12 weeks	Primary: Incidence of bleeding Secondary: Suppression of D-dimer	Primary: Major bleeding events were limited to dabigatran 300 mg plus aspirin-treated patients (four patients out of 64); being statistically different compared to dabigatran 300 mg with no aspirin-treated patients (zero patients out of 150; *P*<0.02). There was a significant difference in major plus clinically relevant bleeding episodes (11 out of 64 vs six out of 105; *P*=0.03) and total bleeding episodes (25 out of 64 vs 14 out of 105; *P*=0.0003) between dabigatran 300 mg plus aspirin- and dabigatran 300 mg with no aspirin-treated patients. The frequency of bleeding in both dabigatran 50 mg treatment groups was significantly lower than that within the warfarin treatment group (seven out of 107 vs 12 out of 70; *P*=0.044). When the doses of dabigatran were compared to each other, irrespective of aspirin use, there were differences in total bleeding episodes in 300 and 150 mg- vs 50 mg-treated patients (37 out of 169 and 30 out of 169 vs seven out of 107; *P*=0.0002 and *P*=0.01, respectively). Secondary: Generally, at 12 weeks, a 13% relative increase of D-dimer plasma measurements was observed in dabigatran 50 mg-treated patients (*P*=0.0008) and a 3% relative increase in dabigatran 150 mg-treated patients (*P*=0.027) was observed. No significant changes in 300 mg dabigatran- (0%; *P*=0.413) or warfarin-treated patients (-1%; *P*=0.267) were seen. Aspirin treatment had no effect on any of these analyses. There were significantly fewer traumatic intracranial hemorrhages in patients receiving either dosage of dabigatran (11 patients for both) compared to patients receiving warfarin (24 patients; (*P*<0.05 for both dabigatran dosages vs warfarin). Fatal traumatic intracranial hemorrhages occurred in five, three and three patients receiving warfarin, dabigatran 150 mg, and 110 mg,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				respectively.
Patel et al[16] ROCKET-AF Rivaroxaban 20 mg QD (15 mg QD in patients with a creatinine clearance 30 to 49 mL/min) vs warfarin (INR of 2.0 to 3.0)	AC, DB, DD, MC, PRO, RCT Patients with nonvalvular AF, as documented on ECG, at moderate- to high-risk for stroke, indicated by a history of stroke, TIA, or systemic embolism or at least two of the following risk factors: heart failure or LVEF ≤35%, hypertension, age ≥75 years, or diabetes mellitus The proportion of patients who had not had a previous ischemic stroke, TIA, or systemic embolism and who had less than two risk factors was limited to 10% of the cohort for each region; the remainder of patients were required to have	N=14,264 590 days (median duration of treatment; 707 days median follow-up)	Primary: Composite of stroke (ischemic or hemorrhagic) and systemic embolism Secondary: Composite of stroke, systemic embolism, or death from cardiovascular causes; composite of stroke, systemic embolism, death from cardiovascular causes, or MI; individual components of composite outcomes; major and nonmajor clinically relevant bleeding events	Primary: In the PP population, stroke or systemic embolism occurred in 188 rivaroxaban-treated patients (1.7% per year) compared to 241 warfarin-treated patients (2.2% per year). Rivaroxaban was non inferior to warfarin in regard to the primary outcome (HR, 0.79; 95% CI, 0.66 to 0.96; *P*<0.001 for non inferiority). In the as-treated safety population, the primary outcome occurred in 189 (1.7% per year) and 243 (2.2% per year) rivaroxaban- and warfarin-treated patients (HR, 0.79; 95% CI, 0.65 to 0.95; *P*=0.01 for superiority). In the ITT population, the primary end point occurred in 269 rivaroxaban-treated patients (2.1% per year) compared to 306 patients in warfarin-treated patients (2.4% per year; HR, 0.88; 95% CI, 0.74 to 1.03; *P*<0.001 for non inferiority; *P*=0.12 for superiority). Secondary: In the on-treatment population, the composite of stroke, systemic embolism, or vascular death occurred in significantly fewer rivaroxaban-treated patients compared to warfarin treated patients (3.11 vs 5.79% per year, respectively; HR, 0.86; 95% CI 0.74 to 0.99; *P*=0.034). In the on-treatment population, the composite of stroke, systemic embolism, vascular death or MI occurred in significantly fewer rivaroxaban-treated patients compared to warfarin treated patients (3.91 vs 4.62% per year, respectively; HR, 0.85; 95% CI 0.74 to 0.96; *P*=0.010). In the on-treatment population, stroke occurred in 184 (2.61%) and 221 (3.12%) rivaroxaban- and warfarin-treated patients; there was no difference in event rates between the two treatments (1.65 vs 1.96% per year; HR, 0.85; 95% CI, 0.70 to 1.03; *P*=0.092). In the on-treatment population, non-central nervous system systemic embolism occurred in five (0.07%) and 22 (0.31%) rivaroxaban- and warfarin-treated patients; the event rate was significantly lower with

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	had either previous thromboembolism or at least three risk factors			rivaroxaban (0.04 vs 0.19% per year; HR, 0.23; 95% CI, 0.09 to 0.61; *P*=0.003). In the on-treatment population, vascular death occurred in 170 (2.41%) and 193 (2.73%) rivaroxaban- and warfarin-treated patients; there was no difference in event rates between the two treatments (1.53 vs 1.71% per year; HR, 0.89; 95% CI, 0.73 to 1.10; *P*=0.289). In the on-treatment population, MI occurred in 101 (1.43%) and 126 (1.78%) rivaroxaban- and warfarin-treated patients; there was no difference in event rates between the two treatments (0.91 vs 1.12% per year; HR, 0.81; 95% CI, 0.63 to 1.06; *P*=0.121). There was no difference in major and clinically relevant nonmajor bleeding between rivaroxaban and warfarin. Bleeding occurred in 1,475 and 1,449 rivaroxaban- and warfarin-treated patients (14.9 and 14.5% per year, respectively; HR, 1.03; 95% CI, 0.96 to 1.11; *P*=0.44). The incidence of major bleeding was similar with rivaroxaban and warfarin (3.6 and 3.4%, respectively; *P*=0.58). Decreases in hemoglobin levels ≥2 g/dL and transfusions were more common among rivaroxaban-treated patients, whereas fatal bleeding and bleeding at critical anatomical sites were less frequent compared to warfarin treated patients. Rates of intracranial hemorrhage were significantly lower with rivaroxaban compared to warfarin (0.5 vs 0.7% per year; HR, 0.67; 95% CI, 0.47 to 0.93; *P*=0.02). Major bleeding from a gastrointestinal site was more common with rivaroxaban, with 224 bleeding events (3.2%), compared to 154 events (2.2%) with warfarin (*P*<0.001).
Hankey et al[45] ROCKET-AF Rivaroxaban 20 mg QD (15 mg QD in patients	Subgroup analysis of ROCKET-AF[12] Patients enrolled in the ROCKET-AF	N=14,264 (previous stroke or TIA; n=7,468)	Primary: Composite of stroke (ischemic or hemorrhagic) and systemic embolism	Primary: The number of events per 100 person-years for the primary endpoint in patients receiving rivaroxaban compared to patients receiving warfarin was consistent among patients with previous stroke or TIA (2.79 vs 2.96%; HR, 0.94; 95% CI, 0.77 to 1.16) and those without (1.44 vs 1.88%; HR, 0.77;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
with a creatinine clearance 30 to 49 mL/min) vs warfarin (INR of 2.0 to 3.0)	trial stratified based on previous stroke and TIA	590 days (median duration of treatment; 707 days median follow-up)	Secondary: Safety, major and nonmajor clinically relevant bleeding events	95% CI, 0.58 to 1.01; *P*=0.23). Secondary: The overall number of adverse events per 100 person-years was similar with both treatments and in patients with and without previous stroke or TIA. The number of major and nonmajor clinically relevant bleeding events per 100 person-years in patients receiving rivaroxaban and warfarin was consistent among patients with previous stroke or TIA (13.31 vs 13.87%; HR, 0.96; 95% CI, 0.87 to 1.07) and those without (16.69 vs 15.19%; HR, 1.10; 95% CI, 0.99 to 1.21; *P*=0.08). The number of major bleeding events per 100 person-years among patients who received at least one dose of study drug was significantly lower among those with previous stroke or TIA (n=318, 3.18%) compared to those without (n=420, 3.89%; HR, 0.81; 95% CI, 0.70 to 0.93; *P*=0.0037), but the safety of rivaroxaban compared to warfarin with respect to major bleeding showed no interaction among patients with (HR, 0.97; 95% CI, 0.79 to 1.19) and without previous stroke or TIA (HR, 1.11; 95% CI, 0.92 to 1.34; *P*=0.36). The effect of rivaroxaban compared to warfarin on intracerebral hemorrhage was consistent among patients with (HR, 0.84; 95% CI, 0.50 to 1.41) and without previous stroke or TIA (HR, 0.46; 95% CI, 0.24 to 0.89; *P*=0.16).
Anderson et al[46] Warfarin (INR ≥2.0) vs placebo, antiplatelet agents (aspirin, aspirin plus clopidogrel, indobufen*), low dose warfarin and low dose warfarin plus aspirin Results for aspirin plus clopidogrel and	MA (15 RCTs) Patients ≥18 years of age with AF or atrial flutter	N=16,058 ≥3 months	Primary: Incidence of systemic embolism and major bleeding Secondary: Not reported	Primary: *Warfarin vs placebo* Four trials compared the efficacy of warfarin vs placebo for prevention of thromboembolic events (n=1,909). Eleven systemic embolic events were observed; two and nine in warfarin- and placebo-treated patients (OR, 0.29; 95% CI, 0.08 to 1.07; *P*=0.06). The rates of major bleeding were higher in warfarin-treated patients in three trials. The combined OR for major bleeding was higher in warfarin-treated patients (OR, 3.01; 95% CI, 1.31 to 6.92; *P*=0.01). *Warfarin vs antiplatelet agents* Nine trials compared the efficacy of warfarin and antiplatelet agents for the prevention of systemic embolism (n=11,756). Thirty four and 71 systemic embolism events occurred in warfarin- and antiplatelet-treated patients (OR, 0.50; 95% CI, 0.33 to 0.75; *P*<0.001). Pooled analysis for the risk of major

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indobufen were not reported.				bleeding showed no evidence of increased risk with warfarin treatment (OR, 1.07; 95% CI, 0.85 to 1.34; *P*=0.59). *Warfarin vs low dose warfarin or a combination of low dose warfarin and aspirin* Five trials compared warfarin vs low dose warfarin or the combination of low dose warfarin and aspirin for the prevention of thromboembolic events. Four trials compared warfarin directly with low dose warfarin (n=1,008), and five and three patients had an embolic event (OR, 1.52; 95% CI, 0.40 to 5.81; *P*=0.54). Two trials compared warfarin to low dose warfarin and aspirin (n=1,385); two patients in each group had a systemic embolic event (OR, 1.00; 95% CI, 0.17 to 5.81; *P*=1.00). The risk of major bleeding was higher in warfarin-treated patients compared to low dose warfarin-treated patients (OR, 2.88; 95% CI, 1.09 to 7.60; *P*=0.03), but there was no difference when comparing warfarin-treated patients to low dose warfarin and aspirin-treated patients (OR, 1.14; 95% CI, 0.55 to 2.36; *P*=0.72). All trials were stopped early owing to the "superiority" of warfarin treatment in stroke prevention seen in other trials. Secondary: Not reported
Agarwal et al[47] Warfarin vs alternative thromboprophylaxis (ximelagatran*, idraparinux*, aspirin, aspirin plus clopidogrel, dabigatran, rivaroxaban, apixaban)	MA (8 RCTs) Patients with nonvalvular AF	N=32,053 (55,789 patient-years) Duration not specified	Primary: Ischemic or hemorrhagic stroke or non-central nervous system embolism Secondary: MI, all-cause mortality, composite adverse vascular events (stroke, non-central nervous system embolism, MI, and death), major bleeding, intracranial	Primary: The rate of stroke or non-central nervous system embolism varied from 1.2 to 2.3% per year. The pooled event rate for stroke or non-central nervous system embolism was calculated to be 1.66% (95% CI, 1.41 to 1.91) per year. There was a significantly higher incidence of stroke and non-central nervous system embolism in patients ≥75 years (2.27% per year) compared to those <75 years of age (1.62% per year; *P*<0.001). A significantly higher pooled incidence of stroke or non-central nervous system embolism in females compared to males (*P*<0.01) and in patients with a history of stroke or TIA compared to patients without previous events (*P*=0.001). Patients with no history of exposure to VKA had a significantly higher incidence of stroke and non-central nervous system embolism compared to patients who reported use of VKA at the time of enrollment (RR, 1.16; 95% CI, 1.01 to 1.33). Pooled analysis stratified by $CHADS_2$ score yielded pooled annual event rates of 0.89% (95% CI, 0.66 to 1.13) per year for scores ≤1, 1.43%

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			hemorrhage, clinically relevant nonmajor bleeding, minor bleeding	(95% CI, 1.19 to 1.66) per year for scores of 2, and 2.50% (95% CI, 2.17 to 2.82) per year for scores ≥3. Compared to with the lowest risk $CHADS_2$ category, the RR of stroke or non-central nervous system embolism was significantly higher with intermediate risk category (RR, 1.46; 95% CI, 1.13 to 1.89; *P*=0.004) and in the high risk category (RR, 2.89; 95% CI, 2.28 to 3.66; *P*<0.001). Secondary: Rates of MI, all-cause mortality, and composite vascular events varied from 0.53 to 1.40% per year, 2.21 to 8.00% per year, and 3.93 to 5.90% per year, respectively. Pooled event rates for MI, all-cause mortality, and composite vascular events were calculated to be 0.76% (95% CI, 0.57 to 0.96) per year, 3.83% (95% CI, 3.07 to 4.58) per year, and 4.80% (95% CI, 4.22 to 5.38) per year, respectively. The incidence of major bleeding episodes ranged from 1.40 to 3.40% per year. The annual rate of intracranial hemorrhage in patients with AF taking warfarin ranged from 0.33 to 0.80% per year. MA of intracranial hemorrhage yielded a pooled event rate of 0.61% (95% CI, 0.48 to 0.73) per year. The cumulative adverse event rate, defined as major vascular events reported or death or major bleedings episodes, was observed to range from 3.00% per year in one trial to 7.64% per year in another.
Saxena et al[48] Oral anticoagulants (warfarin) vs placebo Target INR ranges in patients receiving oral anticoagulants were 2.5 to 4.0 and 1.4 to 2.8 in the two RCTs included in	SR (2 RCTs) Patients with nonrheumatic AF and a previous TIA or minor ischemic stroke	N=485 1.7 to 2.3 years	Primary: Fatal or non-fatal recurrent stroke, all major vascular events (vascular death, recurrent stroke, MI, and systemic embolism), any intracranial bleed, major extracranial bleed Secondary: Not reported	Primary: In one RCT, the annual rate of all vascular events was eight vs 17% in oral anticoagulation and placebo-treated patients. The risk of stroke was reduced from 12 to four percent per year. In absolute terms, 90 vascular events (mainly strokes) were prevented per 1,000 patients treated with oral anticoagulation per year. There were eleven out of 225 nonvascular deaths in oral anticoagulation-treated patients compared to nine out of 214 nonvascular deaths in placebo-treated patients, and 30 out of 225 and 35 out of 214 vascular deaths. In the same trial, the incidence of all bleeding events while receiving oral anticoagulation was low (2.8 vs 0.7% per year). The absolute annual excess of major bleeds was 21 per 1,000 patients treated, with no documented intracerebral bleeding. In the second RCT, four and two placebo- and oral anticoagulation-treated

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
the review.				patients had a recurrent stroke. The number of all vascular events was eight out of 21 in warfarin-treated patients compared to eleven out of 25 in placebo-treated patients (OR, 0.78; 95% CI, 0.20 to 2.9). In the same trial, no intracranial bleeds occurred. Combined results demonstrate that oral anticoagulation is highly effective; it reduces the odds of recurrent stroke (disabling and non-disabling) by two-thirds (OR, 0.36; 95% CI, 0.22 to 0.58) and it almost halves the odds of all vascular events (OR, 0.55; 95% CI, 0.37 to 0.82). The benefit is not negated by an unacceptable increase of major bleeding complications (OR, 4.32; 95% CI, 1.55 to 12.10). In both trials, no intracranial bleeds were reported in oral anticoagulation-treated patients (OR, 0.13; 95% CI, 0.00 to 6.49). Secondary: Not reported
Aguilar et al[49] Oral anticoagulants (warfarin [and congeners*] and orally active DTIs) vs control or placebo	SR (5 RCTs) Patients with AF without prior stroke or TIA	N=2,313 1.5 years (mean follow-up; range, 1.2 to 2.3 years)	Primary: All strokes Secondary: Ischemic strokes, all disabling or fatal stroke, MI, systemic emboli, all intracranial hemorrhage, major extracranial hemorrhage, vascular death, composite of all stroke, MI or vascular death, all-cause mortality	Primary: Consistent reductions were likewise evident in all trials, with an overall OR of 0.39 (95% CI, 0.26 to 0.59). About 25 strokes would be prevented yearly per 1,000 patients given oral anticoagulants. Secondary: Warfarin was associated with a reduction in ischemic stroke in all five trials, which was significant in four (pooled analysis vs control: OR, 0.34; 95% CI, 0.23 to 0.52). With the annualized rate of ischemic stroke in the control group of about four percent per year, the absolute reduction by oral anticoagulants was about 2.6% per year for patients without prior stroke or TIA, or about 25 ischemic strokes saved yearly per 1,000 patients given warfarin. Consistent reductions in all disabling or fatal strokes were seen in all trials, not reaching statistical significance in individual trials but with a significant reduction in pooled analysis (OR, 0.47; 95% CI, 0.28 to 0.80). About 12 of these serious strokes would be prevented yearly for every 1,000 participants given warfarin. Fifteen MIs occurred in three trials; therefore, no meaningful estimate of the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				effect of oral anticoagulants on this outcome could be made (OR, 0.87; 95% CI, 0.32 to 2.42). Ten systemic emboli occurred in the five trials; therefore, no meaningful estimate of the effect of oral anticoagulants could be made, but with the trend similar to that for ischemic stroke (OR, 0.45; 95% CI, 0.13 to 1.57). Seven intracranial hemorrhages occurred, with a nonsignificant trend toward the expected increase (OR, 2.38; 95% CI, 0.54 to 10.50). Major extracranial hemorrhage was similar in warfarin-treated patients, but with wide CIs due to the relatively small number of events (OR, 1.07; 95% CI, 0.53 to 2.12). A nonsignificant trend favoring treatment with warfarin was seen (OR, 0.84; 95% CI, 0.56 to 1.30) for vascular death. For the composite of stroke, MI or vascular death, the OR with oral anticoagulants was 0.57 (95% CI, 0.42 to 0.76). About 25 of these events would be prevented per year for every 1,000 patients given warfarin. Sixty nine and 99 deaths occurred in warfarin- and control-treated patients (OR, 0.69; 95% CI, 0.50 to 0.94). The mortality rate averaged 5% per year in the control group. About 17 deaths would be prevented per year for every 1,000 AF patients given warfarin.
Ezekowitz et al[50] Warfarin vs aspirin vs warfarin plus aspirin	MA (10 trials) Patients with AF	N=not reported 1.2 to 2.3 years (average follow-up)	Primary: Not reported Secondary: Not reported	Primary: Not reported Secondary: Not reported Pooled analysis from the five PC, primary prevention trials demonstrate the value of warfarin for reducing the risk of stroke was consistent among trials and decreased the risk by 68% (4.5 to 1.4% per year) with virtually no increase in the frequency of major bleeding (rates: 1.2, 1.0 and 1.0% per year for warfarin, aspirin and placebo, respectively). Two of these trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
A total of 10 trials were included: five primary prevention PC trials, one secondary prevention trial, one trial comparing warfarin to aspirin, and three trials of warfarin plus aspirin.				evaluated aspirin for the primary prevention of stroke. In one trial, aspirin use was associated with a 42% reduction in stroke and in the other; the reduction of stroke with aspirin compared to placebo was 36%. The primary prevention trials demonstrate that warfarin is "superior" to both aspirin and placebo, with aspirin being more effective than placebo for preventing stroke. The annual rate of the main outcome measures of death due to vascular disease, any stroke, MI or systemic embolism in the secondary prevention trial was 8% per year in warfarin-treated patients and 17% per year in placebo-treated patients. Treatment with warfarin reduced the risk of stroke from 12 to 4% per year (66% reduction). Among the aspirin-treated patients, the incidence of outcome events was 15% per year compared to 19% per year among placebo-treated patients. The incidence of major bleeding was low in this trial: 2.8, 0.9 and 0.7% per year for warfarin, aspirin and placebo. In the trial comparing warfarin to aspirin for the primary prevention of stroke, the primary event rate was 1.3 and 1.9% per year in warfarin- and aspirin-treated patients (RR, 0.67; *P*=0.24), and by ITT analysis there was no benefit from treatment with warfarin. Of note, the trial was not adequately powered to show a difference between the two treatments. Patients >75 years of age had a substantial risk of thromboembolism during treatment with aspirin (4.8% per year); treatment with warfarin reduced the risk to 3.6% per year (RR, 0.73; *P*=0.39). The trial evaluating warfarin in combination with aspirin to warfarin monotherapy in AF patients with at least one prespecified risk factor for thromboembolic disease was terminated after a mean follow-up of 1.1 years because the rate of ischemic stroke and systemic embolization in combination-treated patients was 7.9% per year compared to 1.9% per year in warfarin-treated patients (*P*<0.001). The rates of major bleeding were similar in both treatments.
Reduce the Risk of Death, Recurrent Myocardial Infarction and Thromboembolic Events Such as Stroke or Systemic Embolization After Myocardial Infarction				
Rothberg et al[51] Warfarin (high intensity)	MA (10 RCTs) Patients with ACS	N=5,938 3 months to 4	Primary: MI, stroke, revascularization	Primary: The annualized rate of MI in aspirin-treated patients ranged from 0.03 to 0.93. Nine of the ten trials found a risk reduction attributable to treatment

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
plus aspirin vs aspirin	who were not stented	years (follow-up)	Secondary: Not reported	with warfarin, but only two trials were sufficiently powered for the reduction to reach statistical significance. Reductions in RR ranged from 29 to 100%, with an overall RR of 44%. The annualized risk for ischemic stroke in aspirin-treated patients ranged from 0.000 to 0.080, with a weighted average of 0.008. In the five trials in which at least one stroke was reported, a risk reduction for warfarin plus aspirin-treated patients was found, but only one risk reduction was statistically significant. Reductions in the RR ranged from 50 to 100%, with an overall RR of 54% (CI, 23 to 73). Overall, four hemorrhagic strokes occurred in warfarin-treated patients and one in aspirin-treated patients, translating to one additional intracranial hemorrhage per 1,800 patient-years of combined anticoagulation. The annualized risk for revascularization ranged from 0.076 to 1.300. Five of the seven trials showed decreased rates of percutaneous transluminal coronary angioplasty or CABG for warfarin-treated patients, but only one rate reached statistical significance. HRs ranged from 0.51 to 1.70, with an overall RR reduction of 20% (95% CI, 5 to 33). No trial showed a significant difference in mortality. The combined trials showed a four percent decrease in overall mortality in warfarin-treated patients, but this did not reach significance (*P* value not reported). Nine trials showed an increased risk for major bleeding associated warfarin treatment. The annualized risk for major bleeding in warfarin-treated patients ranged from 0.6 to 18.0%, with an overall risk of 1.5%. The RR for major bleeding with warfarin treatment compared to aspirin was 2.5 (95% CI, 1.7 to 3.7). The RR for minor bleeding was 2.6 (95% CI, 2.0 to 3.3). Secondary: Not reported
Prophylaxis and/or Treatment of Venous Thromboembolism				
Eriksson et al[17] RECORD1	DB, DD, MC, RCT Patients ≥18 years	N=4,541 70 days	Primary: The composite of any DVT, nonfatal PE, or	Primary: Rivaroxaban significantly reduced the risk of the primary composite endpoint (1.1 vs 3.7%; ARR, -2.6%; 95% CI, -3.7 to -1.5; *P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Rivaroxaban 10 mg QD for 35 days vs enoxaparin 40 mg SC QD in the evening for 35 days Rivaroxaban was initiated six to eight hours after wound closure. Enoxaparin was administered 12 hours prior to surgery and then reinitiated six to eight hours after wound closure. All patients received either placebo tablets or placebo injection.	of age undergoing elective total hip replacement		death from any cause up to 36 days; incidence of major bleeding beginning after the first dose of the study drug and up to two days after the last dose of the study drug Secondary: Major VTE (composite of proximal DVT, nonfatal PE, or death from VTE), incidence of DVT (any thrombosis, including both proximal and distal), incidence of symptomatic VTE during treatment and follow-up, death during the follow-up period, any on-treatment bleeding, any on-treatment nonmajor bleeding, hemorrhagic wound complications, any bleeding that started after the first dose and up to two days after the last dose of the study drug, adverse events and death	There was no difference between rivaroxaban and enoxaparin for major bleeding events (0.3 vs 0.1%; *P*=0.18). Secondary: Rivaroxaban significantly reduced the risk of major VTE (0.2 vs 2.0%; ARR, -1.7%; 95% CI, -2.5 to 1.0; *P*<0.001). Rivaroxaban significantly reduced the risk of DVT (0.8 vs 3.4%; ARR, -2.7; 95% CI, -3.7 to -1.7; *P*<0.001). Rivaroxaban and enoxaparin had similar rates of symptomatic VTE during treatment (0.3 vs 0.5%; ARR, -0.2%; 95% CI, -0.6 to 0.1; *P*=0.22) and follow-up (<0.1 vs 0.0%; ARR, -0.1%; 95% CI, -0.4 to 0.1; *P*=0.37). Both treatments had <0.1% cases of death occurring during follow-up (*P* value not reported). Rivaroxaban and enoxaparin had similar rates for any on-treatment bleeding (6.0 vs 5.9%; *P*=0.94) and any on-treatment nonmajor bleeding events (5.8 vs 5.8%; *P* value not reported). The rate of hemorrhagic wound complications was also similar (1.5 vs 1.7%; *P* value not reported). The rate of any bleeding beginning after the first dose of rivaroxaban or placebo were also similar (5.5 vs 5.0%; *P* value not reported). Rivaroxaban and enoxaparin had similar rates of any on-treatment adverse event (64.0 vs 64.7%; *P* value not reported). The incidence of death during the on-treatment period was similar between the two treatments (0.3 vs 0.3%; ARR, 0%; 95% CI, -0.4 to 0.4; *P*=1.00). Of the four deaths that occurred with rivaroxaban, two were possibly related to VTE. Of the four deaths that occurred with enoxaparin, one was related to VTE.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Kakkar et al[18] RECORD2 Rivaroxaban 10 mg QD for 31 to 39 days vs enoxaparin 40 mg SC QD for 10 to 14 days Rivaroxaban was initiated six to eight hours after wound closure. Enoxaparin was administered 12 hours prior to surgery and reinitiated six to eight hours after wound closure. All patients received either placebo tablets or placebo injection.	DB, DD, MC, RCT Patients ≥18 years of age undergoing complete hip replacement	N=2,509 75 days	Primary: The composite of any DVT, nonfatal PE, or death from any cause up to day 30 to 42; incidence of major bleeding beginning after the first dose of the study drug and up to two days after the last dose of the study drug Secondary: Major VTE, (composite of proximal DVT, nonfatal PE, or death from VTE), incidence of DVT (any thrombosis, including both proximal and distal), incidence of symptomatic VTE during treatment and follow-up, death during the follow-up period, any on-treatment bleeding, any on-treatment nonmajor bleeding, hemorrhagic wound complications, any postoperative bleeding that started after the first dose and up to two days after the last dose of the study drug, adverse events	Primary: Rivaroxaban significantly reduced the risk of the primary composite endpoint compared to enoxaparin (2.0 vs 9.3%; ARR, 7.3%; 95% CI, 5.2 to 9.4; *P*<0.0001). Major bleeding occurred at a rate <0.1% with both rivaroxaban and enoxaparin (*P* value not reported). The one major bleeding event with enoxaparin was deemed unrelated to the treatment drug by the adjudication committee. Secondary: Rivaroxaban significantly reduced the risk of major VTE (0.6 vs 5.1%; ARR, 4.5%; 95% CI, 3.0 to 6.0; *P*<0.0001). Rivaroxaban significantly reduced the risk of DVT (1.6 vs 8.2%; ARR, 6.5%; 95% CI, 4.5 to 8.5; *P*<0.0001). Rivaroxaban significantly reduced the risk of on-treatment symptomatic VTE (0.2 vs 1.2%; ARR, 1.0%; 95% CI, 0.3 to 1.8; *P*=0.004); however, the rates during follow-up were similar (0.1 vs 0.2%; ARR, 0.1%; 95% CI, -0.2 to 0.4; *P*=0.62). The incidence of death during the follow-up period was similar between the two treatments (0.0 vs 0.2%; ARR, 0.2%; 95% CI, -0.1 to 0.6; *P*=0.50). Rates of any on-treatment bleeding (6.6 vs 5.5%; *P* value not reported) and any on-treatment nonmajor bleeding (6.5 vs 5.5%; *P* value not reported) were similar between the two treatments. Hemorrhagic wound complications also occurred at similar rates (1.6 vs 1.7%; *P* value not reported). The rate of any bleeding beginning after initiation of rivaroxaban or placebo was also similar (4.7 vs 4.1%; *P* value not reported). Adverse events from any cause were similar between the two treatments (62.5 vs 65.7%; *P* values not reported). The incidence of on-treatment death was similar between the two treatments

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			and death	(0.2 vs 0.7%; ARR, 0.5%; 95% CI, -0.2 to 1.1; *P*=0.29).
Lassen et al[19] RECORD3 Rivaroxaban 10 mg QD for 10 to 14 days vs enoxaparin 40 mg SC QD for 10 to 14 days Rivaroxaban was initiated six to eight hours after wound closure. Enoxaparin as administered 12 hour preoperatively and reinitiated six to eight hours after wound closure. All patients received either placebo tablets or placebo injection.	DB, DD, MC, RCT Patients ≥18 years of age undergoing elective total knee replacement	N=2,531 49 days	Primary: The composite of any DVT, nonfatal PE, or death from any cause within 13 to 17 days post surgery; incidence of major bleeding beginning after the first dose of the study drug and up to two days after the last dose of the study drug Secondary: Major VTE (composite of proximal DVT, nonfatal PE, or death from VTE), incidence of DVT (any thrombosis, including both proximal and distal), incidence of symptomatic VTE during treatment and follow up, death during the follow up period, any on-treatment bleeding or any major bleeding occurring between intake of the first dose of the study medication and two days after the last dose, nonmajor bleeding, adverse events and	Primary: Rivaroxaban significantly reduced the risk of the primary composite endpoint compared to enoxaparin (9.6 vs 18.9%; ARD, -9.2%; 95% CI, -12.4 to -5.9; *P*<0.001). The rate of major bleeding was similar between the two treatments (0.6 vs 0.5%; *P*=0.77). Secondary: Rivaroxaban significantly reduced the risk of major VTE (1.0 vs 2.6%; ARD, -1.6%; 95% CI, -2.8 to -0.4; *P*=0.01). Rivaroxaban significantly reduced the risk of DVT (9.6 vs 18.2%; ARD, -8.4; 95% CI, -11.7 to -5.2; *P*<0.001). Rivaroxaban significantly reduced the risk of on-treatment symptomatic VTE (0.7 vs 2.0%; ARD, -1.3%; 95% CI, -2.2 to -0.4; *P*=0.005); however, during follow-up the rates were similar (0.4 vs 0.2%; ARD, 0.2%; 95% CI, -0.3 to 0.6; *P*=0.44). The incidence of death during follow-up was similar between the two treatments (ARD, -0.2%; 95% CI, -0.6 to 0.2; *P*=0.21). Rates of any on-treatment bleeding (4.9 vs 4.8%; *P*=0.93) or any major bleeding between the start of treatment and two days after the last dose (0.6 vs 0.5%; *P*=0.77) were similar between the two treatments. The rate of nonmajor bleeding was also similar (4.3 vs 4.4%; *P* value not reported). The rates of drug-related adverse events were similar between the two treatments (12 vs 13%; *P* value not reported). The incidence of death during treatment was similar between the two treatments (0.0 vs 0.2%; ARD, -0.2%; 95% CI, -0.8 to 0.2; *P*=0.23)

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			death	
Turpie et al[20] RECORD4 Rivaroxaban 10 mg QD for 10 to 14 days vs enoxaparin 30 mg SC BID for 10 to 14 days Rivaroxaban was initiated six to eight hours after wound closure. Enoxaparin was initiated 12 to 24 hours after wound closure. All patients received either placebo tablets or placebo injection.	DB, DD, MC, RCT Patients ≥18 years of age undergoing total knee replacement	N=3,148 49 days	Primary: The composite of any DVT, nonfatal PE, or death from any cause 17 days after surgery; incidence of major bleeding beginning after the first dose of the study drug and up to two days after the last dose of the study drug Secondary: Major VTE (composite of proximal DVT, nonfatal PE, or death from VTE), incidence of asymptomatic DVT (any thrombosis, including both proximal and distal), incidence of symptomatic VTE during treatment and follow up, death during the follow-up period, clinically relevant nonmajor bleeding, any on-treatment bleeding, any nonmajor bleeding, hemorrhagic wound complications, adverse events and death	Primary: Rivaroxaban significantly reduced the risk of the primary composite endpoint compared to enoxaparin (6.9 vs 10.1%; ARD, -3.19%; 95% CI, -5.67 to -0.71; *P*=0.0118). There was no difference in the rate of major bleeding between the two treatments (0.7 vs 0.3%; *P*=0.1096). Secondary: Rivaroxaban did not reduce the risk of major VTE compared to enoxaparin (1.2 vs 2.0%; ARD, -0.80; 95% CI, -1.34 to 0.60; *P*=0.1237). The rates of asymptomatic DVT were similar between the two treatments (*P* value not reported). Rivaroxaban did not reduce the risk of symptomatic VTE on-treatment (0.7 vs 1.2%; ARD, -0.47; 95% CI, -1.16 to 0.23; *P*=0.1868) or during follow-up (0.2 vs 0.2%; ARD, 0.00%; 95% CI, -0.32 to 0.32; *P*=0.9979). The incidence of death during follow-up was similar between the two treatments (0.3 vs 0.2%; ARD, 0.06%; 95% CI, -0.35 to 0.50; *P*=0.8044). The rates of clinically relevant nonmajor bleeding (10.2 vs 9.2%; *P* value not reported) and any on-treatment bleeding (10.5 vs 9.4%; *P*=0.3287) were similar between the two treatments. The rate of hemorrhagic wound complications was also similar (1.4 vs 1.5%; *P* value not reported). The rates of drug-related adverse events were similar between the two treatments (20.3 vs 19.6%; *P* value not reported). The rates of on-treatment death were similar between the two treatments (0.1 vs 0.2%; *P*=0.7449).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Hutten et al[52] Oral anticoagulants (dicoumarol*, warfarin) Trials were included if different durations of treatment with a VKA were compared. The eight trials compared seven different periods of treatment with VKAs: four weeks vs three months, six vs 12 weeks, six weeks vs six months, three vs six months, three months vs one year, three vs 27 months, and six months vs four years.	SR (8 trials) Patients with symptomatic VTE	N=2,994 Duration varied	Primary: Recurrent VTE Secondary: Major bleeding, mortality	Primary: All trials reported on the occurrence of symptomatic VTE during the period from cessation in VKA-treated patients in the short duration arm until cessation of treatment in the long duration arm. Four trials demonstrated a significant protection from recurrent VTE complications during prolonged treatment with VKAs, while the others revealed a clear trend. In the combined analysis of all eight trials, a significant reduction in thromboembolic events during prolonged treatment was observed (116 out of 1,495 short duration vs 14 out of 1,499 long duration; OR, 0.18; 95% CI, 0.13 to 0.26). Six trials evaluated the incidence of recurrent VTE in the period after cessation of study medication. No trial demonstrated a significant increase in VTE events among participants in the long arm after cessation of treatment, and combined analysis demonstrated similar results (96 out of 1,304 long duration vs 78 out of 1,301 short duration; OR, 1.24; 95% CI, 0.91 to 1.69). Analyses of pooled data demonstrated a significant reduction in recurrent VTE for the following comparisons: four weeks vs three months (OR, 0.23; 95% CI, 0.06 to 0.70), three vs six months (OR, 0.13; 95% CI, 0.05 to 0.33) and three vs 12 months (OR, 0.22; 95% CI, 0.11 to 0.44). Secondary: Four trials reported the incidence of major bleeding during the period from cessation of treatment with VKAs in the short duration arm until cessation of treatment in the long duration arm. No trial demonstrated a significant increase in bleeding complications during prolonged treatment, but combined results demonstrated a significant increase in major bleeding complications during this period (one out of 405 short duration vs eight out of 403 long duration; OR, 4.87; 95% CI, 1.31 to 18.15). Only one trial reported the incidence of major bleeding in the period after cessation of study medication. All trials reported on the occurrence of major bleeding complications for the entire period after randomization until the end of follow-up. No trial demonstrated a significant increase during prolonged treatment, but

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				combined results demonstrated a significant increase during this period (36 out of 1,499 long duration vs 13 out of 1,495 short duration; OR, 2.61; 95% CI, 1.48 to 4.61). Three trials reported mortality during the period from cessation of treatment with VKAs in the short duration arm until cessation of treatment in the long duration arm. One trial demonstrated a non-significant decrease in mortality during prolonged treatment, while the others showed no trends. Combined results demonstrated a non-significant reduction in mortality favoring prolonged treatment (12 out of 188 short duration vs 10 out of 188 long duration; OR, 0.80; 95% CI, 0.34 to 1.91). All trials reported on mortality for the entire period after randomization, with none demonstrating a significant reduction in morality. When the results were combined, a nonsignificant reduction in mortality during the entire study period was observed (71 out of 1,498 long duration vs 75 out of 1,496 short duration; OR, 0.93; 95% CI, 0.67 to 1.30).
van der Heijden et al[53] VKAs vs LMWH	SR (7 RCTs) Patients with symptomatic DVT receiving long-term treatment	N=1,137 3 to 9 months	Primary: Recurrent symptomatic VTE, major bleeding complications, mortality Secondary: Not reported	Primary: All seven trials reported the occurrence of recurrent symptomatic VTE during the first three to six months after randomization. Six trials showed no differences between treatment with LMWH and VKAs, and one trial found a significant OR of 0.38 (95% CI, 0.17 to 0.86) in favor of treatment with LMWH. When the seven trials are combined, the rate of recurrent symptomatic VTE was 6.7 vs 4.8% in VKA- and LMWH-treated patients, corresponding to a nonsignificant reduction in favor of LMWH (OR, 0.70; 95% CI, 0.42 to 1.16). Six trials evaluated the occurrence of recurrent symptomatic VTE during a period of six to nine months after cessation of the allocated treatment. The rate of recurrent symptomatic VTE was 3.5 vs 5.0% of VKA- and LMWH-treated patients, corresponding to nonsignificant difference in favor of VKA treatment (OR, 1.46; 95% CI, 0.80 to 2.69). All seven trials reported the incidence of major bleeding during allocated treatment, with six trials finding no difference between the two treatments and one finding a significant difference in favor of treatment with LMWH

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				(OR, 0.12; 95% CI, 0.02 to 0.89). When the trials were combined, 2.5 vs 0.9% VKA- and LMWH-treated patients had a major bleed; a significant difference in favor of treatment with LMWH (OR, 0.38; 95% CI, 0.15 to 0.94). No major bleeding occurred in the additional nine months of follow-up. All seven trials reported on mortality during the allocated treatment, with the individual trials not finding a significant difference between the two treatments. In the combined analysis, 2.5 vs 3.7% of VKA- and LMWH-treated patients died (OR, 1.51; 95% CI, 0.77 to 2.97). Six trials extended the follow-up period for an additional six to nine months and found that the rate of death was 3.5 vs 3.9% (OR, 1.11; 95% CI, 0.58 to 2.15). Secondary: Not reported
Salazar et al[54] DTI (dabigatran†, desirudin, ximelagatran*) vs warfarin or LMWH (dalteparin, enoxaparin)	SR (12 RCTs) Patients who have undergone total hip replacement or total knee replacement	N=21,642 (efficacy) N=27,360 (safety) Duration varied	Primary: Mortality associated with VTE, incidence of proximal VTE, mortality associated with treatment, appearance of serious hepatopathy, appearance of other serious adverse effects associated with treatment Secondary: Incidence of distal VTE, presence of hepatopathy after treatment, morbidity associated with treatment	Primary and Secondary end points are reported together in the groupings below. *Major, total and symptomatic VTE* Combined analysis from two trials comparing DTIs to LMWH demonstrated that when evaluating the combination of both surgery groups, no difference was observed between the two treatments (557 out of 10,736 vs 392 out of 6,692 events/patients; OR, 0.91; 95% CI, 0.69 to 1.19). Evaluation of the individual surgery groups had similar results. No difference was observed between the two treatments for total VTE (data not reported) or symptomatic VTE (234 out of 12,056 vs 143 out of 7,563; OR, 1.04; 95% CI, 0.84 to 1.29). Combined analysis from three trials comparing ximelagatran to warfarin demonstrated no statistical difference between the two treatments (95 out of 2,498 vs 83 out of 1,829 events/patients; OR, 0.85; 95% CI, 0.63 to 1.15). There were fewer total VTE events in DTI-treated patients (555 out of 2,514 vs 543 out of 1,840; OR, 0.68; 95% CI, 0.59 to 0.78). No difference between the two treatments were observed for symptomatic VTE (47 out of 3,022 vs 48 out of 2,237; OR, 0.80; 95% CI, 0.53 to 1.21). *Major/significant and total bleeding events*

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Combined analysis from eleven trials comparing DTIs to LMWH demonstrated a nonsignificant higher number of major significant bleeding events in DTI-treated patients (334 out of 13,753 vs 138 out of 8,356 events/patients; OR, 1.17; 95% CI, 0.87 to 1.58). In the comparison of each independent dose, only dabigatran 225 mg BID showed more bleeding events in the DTI group (OR, 1.90; 95% CI, 1.05 to 3.44) in the combination of both surgeries and specifically in total hip replacement (26 out of 270 vs 13 out of 270; OR, 2.11; 95% CI, 1.06 to 4.19). Combined analysis from ten trials demonstrated no difference between the two treatments in terms of total bleeding events; however, more events were observed in DTI-treated patients undergoing total hip replacement (2,370 out of 5,949 vs 1,374 out of 4,378; OR, 1.40; 95% CI, 1.06 to 1.85). Combined analysis of three trials comparing ximelagatran to warfarin demonstrated more major/significant bleeding events with ximelagatran, but the difference was not statistically significant (30 out of 3,022 vs 13 out of 2,237 events/patients; OR, 1.76; 95% CI, 0.91 to 3.38). Partial and total bleeding events were very similar to major bleeding events. *All-cause mortality* Combined analysis of eleven trials comparing DTIs to LWMH demonstrated a nonsignificant higher all-cause mortality event rate with DTI treatment (15 out of 13,730 vs four out of 8,335 events/patients; OR, 1.72; 95% CI, 0.68 to 4.35). When including follow-up events the difference met statistical significance (41 out of 13,730 vs 11 out of 8,335; OR, 2.06; 95% CI, 1.10 to 3.87). Combined analysis of three trials comparing ximelagatran to warfarin demonstrated no significant difference between the two treatments (six out of 3,013 vs four out of 2,230 events/patients; OR, 1.19; 95% CI, 0.36 to 4.01), even when follow-up events were included (10 out of 3,013 vs five out of 2,230; OR, 1.62; 95% CI, 0.57 to 4.58). *ALT greater than three times the upper normal limit* The seven trials comparing DTIs to LMWH had high heterogeneity; therefore, results could not be combined. Fewer events were observed in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				DTI-treated patients, but with high heterogeneity, in the ximelagatran trials. No difference was noted when treatment with dabigatran was compared to treatment with LMWH, but these trials had very high heterogeneity. Combined analysis of two trials comparing ximelagatran to warfarin demonstrated no significant difference between the two treatments (18 out of 2,493 vs 21 out of 1,768 events/patients; OR, 0.52; 95% CI, 0.27 to 0.97), even when follow-up events were included (11 out of 2,484 vs one out of 1,783; OR, 5.61; 95% CI, 1.00 to 31.64). *Volume of blood loss* No difference was observed between treatment with DTIs and LMWH in the combined analysis of five trials (n=8,782; WMD, 5.12; 95% CI, -33.81 to 44.04), but these trials had high heterogeneity. No difference was observed between ximelagatran and warfarin in the combined analysis of three trials (n=5,259; WMD, -7.12; 95% CI, -17.08 to 2.84), with no heterogeneity. *Time effect of the beginning of anticoagulation* Trials comparing DTIs to LMWH that began anticoagulation before surgery demonstrated fewer major (OR, 0.54; 95% CI, 0.35 to 0.83) and total (OR, 0.72; 95% CI, 0.63 to 0.82) VTE in DTI-treated patients in both surgery groups. There was also no difference regarding symptomatic VTE. Trials that began anticoagulation after surgery demonstrated more major (OR, 1.68; 95%, 1.12 to 2.52) and total (OR, 1.29; 95% CI, 0.69 to 2.39) VTE events in DTI-treated patients in both surgery groups. Again, there was no difference regarding symptomatic VTE. Trials that began anticoagulation before surgery demonstrated a non-significant greater incidence of major (OR, 1.64; 95% CI, 0.85 to 3.15) and total (OR, 1.45; 95% CI, 0.93 to 2.28) bleeding events in DTI-treated patients in both combined surgeries and in the individual analysis of each surgery. There was no significant difference regarding mortality. *Extended prophylactic anticoagulation vs standard prophylactic*

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				anticoagulation No difference was found in major or total VTE between DTI- and LMWH-treated patients. Symptomatic VTE events in extended anticoagulation occurred more with dabigatran in comparison to LMWH, but the difference was not statistically significant (25 out of 2,293 vs five out of 1,142 events/patients; OR, 2.51; 95% CI, 0.96 to 5.67). In standard anticoagulation, no difference between DTI- and LMWH-treated patients was noted (76 out of 3,351 vs 37 out of 1,542; OR, 0.99; 95% CI, 0.67 to 1.48). Regarding safety, no difference in major or total bleeding events was noted. All-cause mortality, transaminase levels and blood loss were not evaluated.
Brookenthal et al[55] Thromboprophylaxis (aspirin, dextran, heparin [with or without antithrombin III], LMWH [ardeparin*, enoxaparin, tinzaparin], lower extremity pneumatic compression stockings, or warfarin) vs placebo A prophylactic agent of interest was compared to another method of interest or placebo.	MA (14 trials) Patients receiving prophylaxis for ≥7 days for an elective total knee arthroplasty	N=3,482 Duration varied	Primary: Total DVT, proximal DVT, distal DVT, symptomatic PE, fatal PE, minor bleeding, major bleeding, total bleeding, intracranial hemorrhage, non-PE mortality, all-cause mortality Secondary: Not reported	Primary: For total DVT, all treatments, except dextran and aspirin, protected significantly better than placebo (*P*<0.0001). For proximal DVT, no comparison against placebo was available, and rates ranged from 1.7 (aspirin) to 12.8% (SC heparin/antithrombin III). The only significant difference was between treatment with LMWH and warfarin (5.9 vs 10.2%; *P*=0.0002). There was a strong trend that aspirin protected better than warfarin (1.7 vs 10.2%; *P*=0.0106). For distal DVT, no comparison against placebo was available. LMWH (24.4%) protected significantly better than dextran (71.1%; *P*=0.0001), warfarin (35.6%; *P*=0.0001) and aspirin (55.2%; *P*=0.0001). Warfarin (35.6%) protected significantly better than aspirin (55.2%; *P*=0.0045) but worse than SC heparin (21.5%; *P*=0.0029). Aspirin (55.2%) protected significantly less than SC heparin (21.5%; *P*=0.0001) and pneumatic compression stockings (29.5%; *P*=0.0051). Rates of symptomatic PE ranged from 0.0 (aspirin, pneumatic compression stockings and placebo) to 0.4% (warfarin, SC heparin); there was no significant detectable difference among the agents. No fatal PE occurred with any treatment.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The rate of total bleeding ranged from 8.6 (aspirin) to 18.9% (SC heparin). No comparison with placebo was available. The rate of minor bleeding ranged from 8.6 (aspirin) to 18.3% (SC heparin). Rates of major bleeding ranged from 0.0 (aspirin, pneumatic compression stockings) to 2.4% (LWMH), but no difference between treatments were noted. There were no observed intracranial hemorrhages. Rates for overall and non-PE mortality ranged from 0.0 (aspirin, SC heparin, pneumatic compression stockings, placebo, SC heparin/antithrombin III and dextran) to 0.3% (warfarin), but no difference among the treatments were noted. Secondary: Not reported
Cundiff et al[56] Anticoagulants (heparin, phenprocoumon*, warfarin) vs NSAIDs (phenylbutazone*) or placebo	SR (2 RCTs) Patients with DVT or PE	N=113 3 months	Primary: Mortality due to PE, PE, DVT and extension of DVT or both Secondary: All-cause mortality, major hemorrhagic events, fatal hemorrhagic events, morbidity and mortality due to HIT with thrombosis	Data were not pooled because of heterogeneity between the trials, and the trials were too small to determine any difference in mortality, occurrence of PE, and progression or return of DVT between patients receiving anticoagulation and those who were not. Primary: In one trial (n=23), no deaths due to PE were reported and in the other trial (n=90), there was no significant difference in deaths due to PE between anticoagulant- and NSAID-treated patients (one vs zero; RR, 2.63; 95% CI, 0.11 to 62.95). In one trial (n=23), there was no difference in the combined outcome PE, DVT progression or return in anticoagulation-treated patients compared to those who did not receive anticoagulation (five vs five; RR, 1.09; 95% CI, 0.43 to 2.77). In one trial (n=90), there was no difference in the combined outcome recurrent DVT or DVT (18 vs 22; RR, 0.72; 95% CI, 0.45 to 1.14).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: There was no difference in the secondary outcomes of all-cause mortality and major hemorrhage in either trial between the two treatments. Neither trial reported morbidity or mortality due to HIT with thrombosis, or VKA necrosis.
Di Nisio et al[57] Any oral or parenteral anticoagulant (UFH, LMWH, VKA, direct thrombin or factor Xa inhibitors), or both vs inactive control (placebo, no treatment, standard care) or active control	SR (9 RCTs) Ambulatory outpatients of any age with either a solid or hematological cancer, at any stage, and receiving chemotherapy, without a positive history of VTE	N=3,538 Duration varied	Primary: Symptomatic VTE, major bleeding Secondary: Symptomatic PE, symptomatic DVT, asymptomatic VTE, overall VTE, minor bleeding, one year overall mortality, arterial thromboembolic events, superficial thrombophlebitis, quality of life, number of patients experiencing any serious adverse event	Primary: *LMWH vs inactive control* Pooled analysis of six RCTs demonstrated that when compared to placebo, LMWH was associated with a significant reduction symptomatic VTE (RR, 0.62; 95% CI, 0.41 to 0.93), corresponding to a NNT of 60. Pooled analysis of six RCTs suggested a 60% increased risk of a major bleeding (RR, 1.57; 95% CI, 0.69 to 3.60). *LMWH vs active control* In one trial, LMWH was associated with a 67% reduction in symptomatic VTE relative to warfarin (RR, 0.33; 95% CI, 0.14 to 0.83) while the difference with aspirin was not significant (RR, 0.50; 95% CI, 0.19 to 1.31). In one trial, there were no differences between LMWH, aspirin, and warfarin regarding the incidence of major bleeding. *VKA vs inactive control* In one trial, a trend for a reduction in symptomatic VTE (RR, 0.15; 95% CI, 0.02 to 1.20) was reported. There was no significant effect on major bleeding (RR, 0.52; 95% CI, 0.05 to 5.71). *VKA vs active control* One trial reported a nonsignificant difference between VKA and aspirin (RR, 1.50; 95% CI, 0.74 to 3.04). *Antithrombin vs inactive control* In one trial, the effects of antithrombin on symptomatic VTE (RR, 0.84; 95% CI, 0.41 to 1.73) and major bleeding (RR, 0.78; 95% CI, 0.03 to 18.57) were not significant.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: *LMWH vs inactive control* Pooled analysis of six RCTs demonstrated that there was no significant effect on symptomatic PE (RR, 0.63; 95% CI, 0.21 to 1.91) or DVT (RR, 0.60; 95% CO. 0.33 to 1.07). In pooled data from six RCTs, the risk of overall VTE was reduced by 45% with LMWH (RR, 0.55; 95% CI, 0.34 to 0.88) whereas there was no significant benefit or harm for asymptomatic VTE, minor bleeding, one-year mortality, symptomatic arterial thromboembolism, superficial thrombophlebitis, or serious adverse events. None of the six trials considered quality of life, heparin-induced thrombocytopenia, or the incidence of osteoporosis as study incomes. Three trials reported on symptomatic VTE and major bleeding in patient with non-small cell or small cell lung cancer, or both. Pooled analysis showed a nonsignificant 46% reduction in symptomatic VTE (RR, 0.54; 95% CI, 0.27 to 1.09) and a nonsignificant 73% higher risk of major bleeding with LMWH compared to control (RR, 1.73; 95% CI, 0.65 to 4.57). *LMWH vs active control* In one trial, there were no differences between LMWH, aspirin, and warfarin regarding the incidence of symptomatic PE or DVT, minor bleeding, and symptomatic arterial thromboembolism. *VKA vs inactive control* In one trial, there was no significant effect on symptomatic PE (RR, 1.05; 95% CI, 0.07 to 16.58), symptomatic DVT (RR, 0.08; 95% CI, 0.00 to 1.42), or minor bleeding (RR, 2.44; 95% CI, 0.64 to 9.27). No symptomatic arterial thromboembolic events were observed in the VKA or placebo groups. *VKA vs active control and antithrombin vs inactive control* Secondary outcomes were not reported for these comparisons.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Treatment of DVT and PE, and for the reduction in the risk of recurrence of DVT and of PE				
EINSTEIN Investigators et al[21] EINSTEIN-DVT and EINSTEIN-EXT Rivaroxaban 15 mg BID for three weeks followed by 20 mg QD vs enoxaparin 1 mg/kg SC BID plus warfarin or acenocoumarol started within 48 hours of randomization and adjusted to maintain an INR of 2.0 to 3.0 Enoxaparin was discontinued when the INR was ≥2.0 for two consecutive days and the patient had received at least five days of enoxaparin treatment. In the EINSTEIN-EXT trial, patients were randomized to receive rivaroxaban 20 mg QD or placebo for six to 12 months.	AC, MC, OL, NI, RCT (EINSTEIN-DVT) DB, MC, PC, RCT (EINSTEIN-EXT) Patients with acute, symptomatic, objectively confirmed proximal DVT without symptomatic PE; for enrollment into the extension phase, patients had objectively confirmed symptomatic DVT or PE and had been treated for six to 12 months with rivaroxaban or acenocoumarol or warfarin (in the EINSTEIN studies or from routine care)	N=3,449 Up to 12 months (both studies)	Primary: Symptomatic, recurrent VTE (composite of DVT or nonfatal or fatal PE), clinically relevant bleeding (EINSTEIN-DVT) or major bleeding (EINSTEIN-EXT) Secondary: All-cause mortality, vascular events (ACS, ischemic stroke, TIA, or systemic embolism), and net clinical benefit (composite of the primary efficacy outcome or major bleeding)	Primary: *EINSTEIN-DVT* A symptomatic, recurrent VTE occurred in 2.1% of patients treated with rivaroxaban and 3.0% of patients receiving standard therapy with enoxaparin (HR, 0.68; 95% CI, 0.44 to 1.04; *P*<0.001 for non inferiority, and *P*=0.08 for superiority). There was no statistically significant difference in the occurrence of clinically relevant (first major or clinically relevant nonmajor) bleeding between patients receiving rivaroxaban or standard therapy with enoxaparin (8.1% for both, HR, 0.97; 95% CI, 0.76 to 1.22; *P*=0.77). *EINSTEIN-EXT* Symptomatic, recurrent VTE occurred in eight patients in the rivaroxaban group and 42 patients in the placebo group (1.3 vs 7.1%; HR, 0.18; 95% CI, 0.09 to 0.39; *P*<0.001). Major bleeding occurred in four patients in the rivaroxaban group and zero patients in the placebo group (*P*=0.11). Secondary: *EINSTEIN-DVT* All-cause mortality was similar between patients treated with rivaroxaban or standard therapy with enoxaparin (2.2 vs 2.9%, respectively; HR, 0.67; 95% CI, 0.44 to 1.02; *P*=0.06). There was no statistically significant difference in vascular events between patients receiving rivaroxaban or standard therapy with enoxaparin (0.7 vs 0.8%, respectively; HR, 0.79; 95% CI, 0.36 to 1.71; *P*=0.55). There was a significantly greater net clinical benefit with rivaroxaban compared to standard therapy with enoxaparin (2.9 vs 4.2%; HR, 0.67; 95% CI, 0.47 to 0.95; *P*=0.03). *EINSTEIN-EXT* There was one death in the rivaroxaban treatment group and two deaths in the placebo group during follow up (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				There was no statistically significant difference in vascular events between patients receiving treatment with rivaroxaban or placebo (0.5 vs 0.7%, respectively; HR, 0.74; 95% CI, 0.17 to 3.3; *P*=0.69). There was a significantly greater net clinical benefit in patients who received rivaroxaban compared to placebo (2.0 vs 7.1%; HR, 0.28; 95% CI, 0.15 to 0.53; *P*<0.001).
EINSTEIN PE Investigators et al[22] EINSTEIN-PE Rivaroxaban 15 mg BID for three weeks followed by 20 mg QD vs enoxaparin 1 mg/kg SC BID plus warfarin or acenocoumarol started within 48 hours of randomization and adjusted to maintain an INR of 2.0 to 3.0 Enoxaparin was discontinued when the INR was ≥2.0 for two consecutive days and the patient had received at least five days of enoxaparin treatment.	AC, MC, NI, OL, RCT Patients with an acute, symptomatic PE with objective confirmation, with or without symptomatic DVT Patients were ineligible if they had received a therapeutic dose of LMWH, fondaparinux, or UFH for more than 48 hours or if they had received more than a single dose of a VKA before randomization.	N=4,832 Up to 12 months	Primary: Symptomatic, recurrent VTE (composite of DVT or nonfatal or fatal PE) and clinically relevant bleeding Secondary: Major bleeding, death from any cause, vascular events (ACS, ischemic stroke, TIA, or systemic embolism) and net clinical benefit (composite of the primary efficacy outcome and major bleeding)	Primary: Symptomatic, recurrent VTE occurred in 50 patients (2.1%) receiving rivaroxaban and 44 patients (1.8%) receiving standard therapy with enoxaparin (HR, 1.12; 95% CI, 0.75 to 1.68; *P*=0.003 for non inferiority and *P*=0.57 for superiority). Recurrent, nonfatal VTE was suspected in 491 patients in the rivaroxaban group and in 453 patients in the standard therapy group. Major or clinically relevant nonmajor bleeding occurred in 249 patients (10.3%) receiving rivaroxaban and 274 patients (11.4%) receiving standard therapy with enoxaparin (HR, 0.90; 95% CI, 0.76 to 1.07; *P*=0.23). Secondary: Major bleeding occurred in 26 patients (1.1%) receiving rivaroxaban treatment compared to 52 patients (2.2%) receiving standard therapy with enoxaparin (HR, 0.49; 95% CI, 0.31 to 0.79, *P*=0.003). There was no statistically significant difference in death from any cause between patients receiving rivaroxaban or standard therapy (2.4 vs 2.1%, respectively, HR, 1.13; 95% CI, 0.77 to 1.65; *P*=0.53). Fifteen patients in the rivaroxaban group and 21 patients in the standard therapy group experienced an acute coronary event (*P* value not reported). A cerebrovascular event was reported in 12 and 13 patients receiving rivaroxaban or standard therapy with enoxaparin, respectively (*P* value not reported). A systemic embolism occurred in five patients receiving rivaroxaban and three patients receiving standard therapy (*P* value not

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				reported). A net clinical benefit was reported in 83 patients (3.4%) in the rivaroxaban group and 96 patients (4.0%) in the standard therapy group (HR, 0.85; 95% CI, 0.63 to 1.14; *P*=0.28).
Safety				
Uchino et al[46] Dabigatran vs control (warfarin, enoxaparin, or placebo)	MA (7 RCTs; 2 trials of stroke prophylaxis in AF, 1 trial in acute VTE, 1 in ACS, and 3 of short term prophylaxis in DVT) Patient population not specified	N=30,514 Duration not specified	Primary: Acute coronary events (MI or ACS) Secondary: Overall mortality	Primary: Dabigatran was significantly associated with a higher risk of MI or ACS compared to control (237/20,000 [1.19%] vs 83/10,514 [0.79%]; OR, 1.33; 95% CI, 1.03 to 1.71; *P*=0.03). The risk of MI or ACS was similar when using revised RE-LY trial results (OR, 1.27; 95% CI, 1.00 to 1.61; *P*=0.05) or after exclusion of short term trials (OR, 1.33; 95% CI, 1.03 to 1.72; *P*=0.03). No relationship between the baseline risk of acute coronary events and the OR for acute coronary events associated with dabigatran use (*P*=0.61). Secondary: Six trials reported on overall mortality. Dabigatran was significantly associated with lower mortality compared to control (945/19,555 [4.83%] vs 524/10,444 [5.02%]; OR, 0.89; 95% CI, 0.80 to 0.99; *P*=0.04).

*Not available in the United States.
†Not Food and Drug Administration approved for this indication.
Drug regimen abbreviations: BID=twice daily, SC=subcutaneous, QD=once daily
Study abbreviations: AC=active control, ARD=absolute risk difference, ARR=absolute risk reduction, CI=confidence interval, DB=double-blind, DD=double dummy, HR=hazard ratio, ITT=intention-to-treat, MA=meta analysis, MC=multicenter, NI=non inferiority, NNT=number needed to treat, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel group, PP=per-protocol, PRO=prospective, RCT=randomized controlled trial, RR=relative risk, SR=systematic review, WMD=weighted mean difference
Miscellaneous abbreviations: ACS=acute coronary syndrome, AF=atrial fibrillation, ALT=alanine transaminase, CABG=coronary artery bypass graft surgery, CAD=coronary artery disease, cTTR=center's mean time in therapeutic range, DTI=direct thrombin inhibitor, DVT=deep vein thrombosis, ECG=electrocardiogram, GUSTO= Global Utilization Of Streptokinase and Tpa For Occluded Arteries, HIT=heparin induced thrombocytopenia, INR=International Normalized Ratio, LMWH=low molecular weight heparin, LVEF=left ventricular ejection fraction, MI=myocardial infarction, NSAID=nonsteroidal anti-inflammatory drug, NYHA=New York Heart Association, PE=pulmonary embolism, TIA=transient ischemic attack, TIMI=Thrombolysis in Myocardial Infarction, TTR=time in therapeutic range, UFH=unfractionated heparin, VKA=vitamin k antagonist, VTE=venous thromboembolism

Special Populations

Table 5. Special Populations[1-4,6,7]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Apixaban	Dose adjustment is required; a dose of 2.5 mg and a dosing frequency of twice daily are recommended for subjects with any two of the following: age ≥80 years, body weight ≤60 kg or serum creatinine ≥1.5 mg/dL. Safety and efficacy in children have not been established.	Renal dose adjustment is required; for a serum creatinine ≥1.5 mg/dL, a dose of 2.5 mg and a dosing frequency of twice daily are recommended.	No dosage adjustment required in mild hepatic impairment. Not recommended for use in patients with severe hepatic impairment.	B	Unknown
Dabigatran etexilate mesylate	No dosage adjustment required in the elderly. Safety and efficacy in children have not been established.	Renal dose adjustment is required; for creatinine clearances 15 to 30 mL/minute, a dose of 75 mg and a dosing frequency of twice daily are recommended. Dosing recommendations for patients with creatinine clearance <15 mL/minute or on dialysis cannot be provided. Discontinue in patients who develop acute renal failure while receiving therapy and consider alternative anticoagulant	Not reported	C	Unknown

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
		therapy.			
Rivaroxaban	No dosage adjustment required in the elderly. Safety and efficacy in children have not been established.	Renal dose adjustment is required; for creatinine clearances 15 to 50 mL/minute, a dose of 15 mg is recommended (atrial fibrillation only). Avoid use in patients with severe renal dysfunction (creatinine clearance <30 mL/minute).*	No dosage adjustment required. Avoid use in patients with moderate or severe hepatic dysfunction or with any hepatic disease associated with coagulopathy.	C	Unknown
Warfarin	Caution should be observed with administration to elderly patients in any situation or physical condition where added risk of hemorrhage is present. Safety and efficacy in children have not been established.†	No dose adjustment required.	No dosage adjustment required. Hepatic dysfunction can potentiate the response to warfarin through impaired synthesis of clotting factors and decreased metabolism of warfarin.	X	Not reported

*Restriction does not apply when being used for the management of nonvalvular atrial fibrillation.
†The use of warfarin in pediatric patients is well documented for the prevention and treatment of thromboembolic events.

Adverse Drug Events

Table 6. Bleeding Events in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE[1]

Bleeding Event	Reported Frequency	
	Apixaban n (%/year), N=9,088	Warfarin n (%/year), N=9,052
Clinically relevant nonmajor bleeding	318 (2.08)	444 (3.00)
Fatal bleeding*	10 (0.06)	37 (0.24)
Gastrointestinal bleeding†	128 (0.83)	141 (0.93)
Intracranial bleeding	52 (0.33)	123 (0.82)
Intraocular bleeding‡	32 (0.21)	22 (0.14)
Major bleeding§	327 (2.13)	462 (3.09)

* Fatal bleed is an adjudicated death because of bleeding during the treatment period and includes both fatal extracranial bleeds and fatal hemorrhagic stroke.
†Gastrointestinal bleed includes upper gastrointestinal, lower gastrointestinal and rectal bleeding.

‡Intraocular bleed is within the corpus of the eye (a conjunctival bleed is not an intraocular bleed).
§International Society on Thrombosis and Hemostasis major bleed assessed by sequential testing strategy for superiority designed to control the overall type I error in the trial.

Table 7. Bleeding Events in the RE-LY Trial (per 100 Patient Years)*[2]

Bleeding Event	Reported Frequency	
	Dabigatran Etexilate Mesylate, 150 mg Twice Daily; n (%), N=6,067	Warfarin; n (%), N=6,022
Any bleed	1,993 (16.6)	2,166 (18.4)
Intracranial hemorrhage	38 (0.3)	90 (0.8)
Life-threatening bleed	179 (1.5)	218 (1.9)
Major bleed	399 (3.3)	421 (3.6)

*Patients contributed multiple events and events were counted in multiple categories.

Table 8. Bleeding Events in the ROCKET-AF Trial (per 100 Patient Years)*[3]

Bleeding Event	Reported Frequency	
	Rivaroxaban, n (%), N=7,111	Warfarin n (%), N=7,125
Bleeding into critical organ*	91 (0.8)	133 (1.2)
Bleeding requiring ≥2 units of whole or packed red blood cells	183 (1.7)	149 (1.3)
Fatal bleeding	27 (0.2)	55 (0.5)
Gastrointestinal bleeding	221 (2)	140 (1.2)
Major bleeding†	395 (3.6)	386 (3.5)

*The majority of the events were intracranial, but also included intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome or retroperitoneal.
†Defined as clinically overt bleeding associated with a decrease in hemoglobin of at least 2 g/dL, transfusion of at least two units of packed red blood cells or whole blood, bleeding at a critical site, or with a fatal outcome. Hemorrhagic strokes are counted as both bleeding and efficacy events. Major bleeding events excluding strokes are 3.3 per 100 patient years for rivaroxaban vs 2.9 per 100 patient years for warfarin.

Table 9. Bleeding Events in the RECORD1, RECORD2 and RECORD3 Trials* (%)[3]

Bleeding Event(s)	Rivaroxaban n (%)	Enoxaparin† n (%)
Total Patients	**N=4,487**	**N=4,524**
Any bleeding event‡	261 (5.8)	251 (5.6)
Major bleeding event	14 (0.3)	9 (0.2)
• Bleeding into a critical organ	2 (<0.1)	3 (0.1)
• Bleeding that required re-operation	7 (0.2)	5 (0.1)
• Extra-surgical site bleeding requiring transfusion of >2 units of whole blood or packed cells	4 (0.1)	1 (<0.1)
• Fatal bleeding	1 (<0.1)	0
Hip Surgery	**N=3,281**	**N=3,298**
Any bleeding event‡	201 (6.1)	191 (5.8)
Major bleeding event	7 (0.2)	3 (0.1)
• Bleeding into a critical organ	1 (<0.1)	1 (<0.1)
• Bleeding that required re-operation	2 (0.1)	1 (<0.1)
• Extra-surgical site bleeding required transfusion of >2 units of whole blood or packed cells	3 (0.1)	1 (<0.1)
• Fatal bleeding	1 (<0.1)	0
Knee Surgery	**N=1,206**	**N=1,226**
Any bleeding event‡	60 (5)	60 (4.9)
Major bleeding event	7 (0.6)	6 (0.5)
• Bleeding into a critical organ	1 (0.1)	2 (0.2)
• Bleeding that required reoperation	5 (0.4)	4 (0.3)

Bleeding Event(s)	Rivaroxaban n (%)	Enoxaparin† n (%)
Total Patients	**N=4,487**	**N=4,524**
• Extra-surgical site bleeding required transfusion of >2 units of whole blood or packed cells	1 (0.1)	0
• Fatal bleeding	0	0

*Bleeding events occurring any time following the first dose of double-blind study medication (which may have been prior to administration of active drug) until two days after the last dose of the double-blind study medication. Patients may have more than one event.
†Includes the placebo-controlled period for RECORD2, enoxaparin dosing was 40 mg once daily (RECORD1 to 3).
‡Includes major bleeding events.

Table 10. Bleeding Events in the Pooled Analysis of EINSTEIN-DVT and EINSTEIN-PE Trials*[3]

Bleeding Event	Reported Frequency	
	Rivaroxaban† n (%), N=4,130	Enoxaparin/Vitamin K Antagonist n (%), N=4,416
Major bleeding	40 (1.0)	72 (1.7)
• Fatal bleeding	3 (<0.1)	8 (0.2)
o Intracranial	2 (<0.1)	4 (<0.1)
• Nonfatal critical organ bleeding	10 (0.2)	29 (0.7)
o Intraarticular‡	0	4 (<0.1)
o Intracranial‡	3 (<0.1)	10 (0.2)
o Intraocular‡	3 (<0.1)	2 (<0.1)
o Retroperitoneal‡	1 (<0.1)	8 (0.2)
• Nonfatal critical organ bleeding§	27 (0.7)	37 (0.9)
• Decreased hemoglobin ≥2g/dL	28 (0.7)	42 (1.0)
• Transfusion of ≥2 units of whole blood or packed red blood cells	18 (0.4)	25 (0.6)
Clinically relevant nonmajor bleeding	357 (8.6)	359 (8.7)
Any bleeding	1,169 (28.3)	1,153 (28)

*Bleeding event occurred after randomization and up to two days after the last dose of study drug. Although a patient may have had two or more events, the patient is counted only once in a category.
†Patients in the EINSTEIN DVT and EINSTEIN PE trials received rivaroxaban 15 mg twice daily for three weeks followed by 20 mg once daily or enoxaparin 1 mg/kg twice daily then vitamin K antagonist titrated doses to achieve a target International Normalized Ratio of 2.5.
‡Treatment-emergent major bleeding events with at least two subjects in any pooled treatment group.
§Major bleeding which is not fatal or in a critical organ, but resulting in a decrease in hemoglobin of at least 2 g/dL and/or transfusion of two or more units of whole blood or packed red blood cells.

Table 11. Bleeding Events in EINSTEIN-EXT Trial*[3]

Bleeding Event	Reported Frequency	
	Rivaroxaban† n (%), N=598	Placebo† n (%), N=590
Any bleeding	104 (17.4)	63 (10.7)
Clinically relevant nonmajor bleeding	32 (5.4)	7 (1.2)
Major bleeding‡	4 (0.7)	0
• Decreased hemoglobin ≥2g/dL	4 (0.7)	0
• Gastrointestinal	3 (0.5)	0
• Menorrhagia	1 (0.2)	0
• Transfusion of ≥2 units of whole blood or packed red blood cells	2 (0.2)	0

*Bleeding event occurred after randomization and up to two days after the last dose of study drug. Although a patient may have had two or more events, the patient is counted only once in a category.
† Patients in the EINSTEIN extension trial received rivaroxaban 20 mg once daily or placebo.
‡ There were no fatal or critical organ bleeding events.

Table 12. Adverse Events[4,6,7]

Adverse Event	Warfarin
Abdominal pain	✔
Alopecia	✔
Bloating	✔
Chills	✔
Cholestatic hepatitis	✔
Cholesterol microemboli	✔
Dermatitis	✔
Diarrhea	✔
Elevated liver enzymes	✔
Flatulence	✔
Hemorrhage	✔
Hepatitis	✔
Hypersensitivity/allergic reactions	✔
Nausea	✔
Necrosis of the skin	✔
Pruritus	✔
Rash	✔
Systemic atheroemboli	✔
Taste perversion	✔
Tracheal or tracheobronchial calcification	✔
Vomiting	✔

✔ Percent not specified.

The risk of major bleeds was similar with dabigatran etexilate mesylate 150 mg and warfarin across major subgroups defined by baseline characteristics, with the exception of age, where there was a trend towards a higher incidence of major bleeding on dabigatran etexilate mesylate (hazard ratio [HR], 1.2; 95% confidence interval [CI], 1.0 to 1.4) for patients ≥75 years of age. There was a higher rate of major gastrointestinal bleeds and any gastrointestinal bleeds in patients receiving dabigatran etexilate mesylate 150 mg than in patients receiving warfarin (1.6 vs 1.1%, respectively; HR, 1.5; 95% CI, 1.2 to 1.9; and 6.1 vs 4.0%, respectively). In addition, patients receiving dabigatran etexilate mesylate 150 mg had an increased incidence of gastrointestinal adverse reactions compared to patients receiving warfarin (35 vs 24%).[1]

Adverse events occurring more often with rivaroxaban compared to placebo include abdominal pain, dyspepsia, fatigue, sinusitis, toothache and urinary tract infection. Compared to patients treated with enoxaparin, patients treated with rivaroxaban reported a higher incidence of blisters, muscle spasms, pain in extremities, pruritus, and syncope and wound secretions.[3,6,7]

In the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial, (ARISTOTLE), the incidence of major bleeding was consistent across most major subgroups including age, weight, $CHADS_2$ score, prior warfarin use, geographic region and aspirin use at randomization. Patients with diabetes who received apixaban had a higher incidence of bleeding compared to patients without diabetes (3.0 vs 1.9% per year). In the Apixaban Vs Acetylsalicylic acid (ASA) to Prevent Strokes (AVERROES) trial, there was no difference in the incidence of major bleeding between patients randomized to receive apixaban or ASA (*P*=0.07). Moreover, the incidence of fatal (HR, 0.99; 95% CI, 0.23 to 4.29) or intracranial bleeds (HR, 0.99; 95% CI, 0.39 to 2.51) did not differ significantly between the treatments. Hypersensitivity reactions (hypersensitivity, skin rash and anaphylactic reactions) and syncope have been reported in <1% of patients treated with apixaban.

Contraindications

Table 13. Contraindications[1-4,6,7]

Contraindication	Apixaban	Dabigatran Etexilate Mesylate	Rivaroxaban	Warfarin
Active pathological bleeds	✔	✔	✔	-
Bleeding tendencies	-	-	-	✔
Hemorrhagic tendencies or blood dyscrasias	-	-	-	✔
Hypersensitivity to any component of the product	✔	✔	✔	-
Major regional or lumbar block anesthesia	-	-	-	✔
Malignant hypertension	-	-	-	✔
Mechanical prosthetic heart valves	-	✔	-	-
Pregnancy	-	-	-	✔
Recent or contemplated surgery of the central nervous system or eye, or traumatic surgery resulting in large open surfaces	-	-	-	✔
Spinal puncture and other diagnostic or therapeutic procedures with potential for uncontrollable bleeding	-	-	-	✔
Threatened abortion, eclampsia and preeclampsia	-	-	-	✔
Unsupervised patients with conditions associated with potential high level of non-compliance	-	-	-	✔

Black Box Warning for Apixaban (Eliquis®)[1]

WARNING
Discontinuation in patients with nonvalvular atrial fibrillation: Discontinuing apixaban places patients at an increased risk of thrombotic events. An increased rate of stroke was observed following discontinuation of apixaban in clinical trials in patients with nonvalvular atrial fibrillation. If apixaban must be discontinued for a reason other than pathological bleeding, coverage with another anticoagulant should be strongly considered.

Black Box Warning for rivaroxaban (Xarelto®)[3]

WARNING
Discontinuation in patients with nonvalvular atrial fibrillation: Discontinuing rivaroxaban places patients at an increased risk of thrombotic events. To reduce this risk, consider administering another anticoagulant if rivaroxaban must be discontinued for a reason other than pathological bleeding. Hematomas: Epidural or spinal hematomas have occurred in patients treated with rivaroxaban who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Monitor patients frequently for signs and symptoms of neurological impairment and if observed, treat urgently. Consider the benefits and risks before neuraxial intervention in patients who are or who need to be anticoagulated.

Black Box Warning for warfarin (Coumadin®, Jantoven®)[4]

WARNING
Bleeding risk: Warfarin can cause major or fatal bleeding. Bleeding is more likely to occur during the starting period and with a higher dose (resulting in a higher international normalized ratio [INR]). Risk factors for bleeding include high intensity of anticoagulation (INR >4), ≥65 years of age, highly variable INRs, history of gastrointestinal bleeding, hypertension, cerebrovascular disease, serious heart disease, anemia, malignancy, trauma, renal function impairment, concomitant drugs and long duration of warfarin therapy. Regular monitoring of INR should be performed on all treated patients. Those at high risk of bleeding may benefit from more frequent INR monitoring, careful dose adjustment to desired INR and a shorter duration of therapy. Patients should be instructed about prevention measures to minimize risk of bleeding and to report immediately to health care provider signs and symptoms of bleeding.

Warnings/Precautions

Table 14. Warnings and Precautions[1-4,6,7]

Warning/Precaution	Apixaban	Dabigatran Etexilate Mesylate	Rivaroxaban	Warfarin
Avoid strong P-glycoprotein and CYP3A4 inducers or inhibitors	-	-	✔	-
Deficiency in protein C-mediated anticoagulant response	-	-	-	✔
Diabetes mellitus; risk of therapy may be increased	-	-	-	✔
Eye surgery; minor complications of sharp needle and local anesthesia block have been reported	-	-	-	✔
Heparin-induced thrombocytopenia; treatment may be considered after platelet count has normalized	-	-	-	✔
Females of reproductive potential; may cause pregnancy loss, birth defects or fetal death	-	-	-	✔
Increased risk of stroke after discontinuing treatment in nonvalvular atrial fibrillation	✔	✔	✔	-
Increased risk of bleeding and may cause serious or fatal bleeding	✔	✔	✔	✔
Infectious diseases or disturbances of intestinal flora	-	-	-	✔
Moderate to severe hepatic impairment; risk of therapy may be increased	-	-	-	✔
Moderate to severe hypertension; risk of therapy may be increased	-	-	-	✔
Patients with renal impairment	-	-	✔	-

Warning/Precaution	Apixaban	Dabigatran Etexilate Mesylate	Rivaroxaban	Warfarin
(creatinine clearance of <30 or <15 mL/minute [atrial fibrillation only])				
Polycythemia vera; risk of therapy may be increased	-	-	-	✔
Pregnant women; risk of pregnancy-related hemorrhage has not been evaluated	-	-	✔	-
Prosthetic heart valves; not evaluated in this population	✔	-	-	-
Risk of epidural or spinal hematoma when neuraxial anesthesia or spinal puncture is employed in anticoagulated patients	-	-	✔	-
Strong P-glycoprotein inducers reduce drug exposure	-	✔	-	-
Thromboembolic and bleeding events in patients with prosthetic heart valves	-	✔	-	-
Tissue necrosis or gangrene of the skin has been reported	-	-	-	✔
Systemic atheroemboli and cholesterol microemboli; discontinue treatment if such phenomena is observed	-	-	-	✔
Use of an indwelling catheter; risk of therapy may be increased	-	-	-	✔
Use in pregnant women with mechanical heart valves; potential benefits may outweigh the risks for pregnant women with mechanical heart valves at high risk of thromboembolism	-	-	-	✔
Vasculitis; risk of therapy may be increased	-	-	-	✔

Drug Interactions

Table 15. Drug Interactions[1-4,6,7]

Generic Name	Interacting Medication or Disease	Potential Result
Oral anticoagulants (apixaban, dabigatran etexilate mesylate, rivaroxaban)	P-glycoprotein inducers (i.e., rifampin)	The exposure of the oral anticoagulant may be decreased, resulting in decreased therapeutic effects.
Oral anticoagulants (apixaban, rivaroxaban,	Salicylates	The risk of bleeding may be increased. The adverse reactions of aspirin on gastric mucosa and platelet function also may enhance the possibility of

Generic Name	Interacting Medication or Disease	Potential Result
warfarin)		hemorrhage.
Oral anticoagulants (apixaban, rivaroxaban)	Clopidogrel	The risk of bleeding may be increased, and bleeding time may be increased.
Oral anticoagulants (apixaban, rivaroxaban)	Dabigatran etexilate mesylate	The risk of bleeding may be increased.
Oral anticoagulants (apixaban, rivaroxaban)	Heparins	Additive effects on anti-factor Xa activity and the risk of bleeding may be increased.
Oral anticoagulants (apixaban, rivaroxaban)	P-glycoprotein inhibitors (i.e., clarithromycin)	The exposure of the oral anticoagulant may be increased, resulting in increased therapeutic effects and risk of bleeding.
Oral anticoagulants (apixaban, rivaroxaban)	Strong cytochrome P450 3A4 inhibitors (i.e., ketoconazole)	The exposure of the oral anticoagulant may be increased, resulting in increased therapeutic effects and risk of bleeding.
Oral anticoagulants (apixaban, rivaroxaban)	Warfarin	The risk of bleeding may be increased.
Oral anticoagulants (apixaban, warfarin)	Alteplase	The risk of serious bleeding may be increased.
Oral anticoagulants (apixaban)	Strong cytochrome P450 3A4 inducers (i.e., ketoconazole)	The exposure of the oral anticoagulant may be decreased, resulting in decreased therapeutic effects.
Oral anticoagulants (rivaroxaban)	Nonsteroidal anti-inflammatory drugs	Nonsteroidal anti-inflammatory drugs are known to increase bleeding, and bleeding risk may be increased when rivaroxaban is given concomitantly.
Oral anticoagulants (warfarin)	Acetaminophen	Acetaminophen appears to increase the antithrombotic effect of warfarin in a dose-dependent manner.
Oral anticoagulants (warfarin)	Aminoglutethimide	Warfarin's action to decrease prothrombin levels may be reduced.
Oral anticoagulants (warfarin)	Amiodarone	The hypoprothrombinemic effect of warfarin is augmented.
Oral anticoagulants (warfarin)	Androgens (17-alkyl derivatives)	The hypoprothrombinemic effect of warfarin is potentiated.
Oral anticoagulants (warfarin)	Antineoplastic agents	The anticoagulant effect of warfarin may be increased.
Oral anticoagulants (warfarin)	Argatroban	The risk of bleeding may be increased due to abnormal prolongation of the prothrombin time and International Normalized Ratio.
Oral anticoagulants (warfarin)	Azole antifungals	The anticoagulant effect of warfarin may be increased.
Oral anticoagulants (warfarin)	Barbiturates	The effects of warfarin may be decreased.
Oral anticoagulants (warfarin)	Bosentan	The effects of warfarin may be decreased.
Oral anticoagulants (warfarin)	Carbamazepine	The effects of warfarin may be decreased.
Oral anticoagulants (warfarin)	Cephalosporins	The effects of warfarin may be increased.

Generic Name	Interacting Medication or Disease	Potential Result
Oral anticoagulants (warfarin)	Chloramphenicol	The effects of warfarin may be increased.
Oral anticoagulants (warfarin)	Cholestyramine	The effects of warfarin may be decreased.
Oral anticoagulants (warfarin)	Corticosteroids	The anticoagulant dose requirements may be reduced. Corticosteroids may induce hypercoagulation that could oppose warfarin actions.
Oral anticoagulants (warfarin)	Dextrothyroxine	The hypoprothrombinemic effect of warfarin is increased.
Oral anticoagulants (warfarin)	Disulfiram	The effects of warfarin may be increased.
Oral anticoagulants (warfarin)	Ethchlorvynol	The hypoprothrombinemic effect of warfarin is decreased.
Oral anticoagulants (warfarin)	Fibric acids	The hypoprothrombinemic effect of warfarin is increased.
Oral anticoagulants (warfarin)	Gefitinib	The effects of warfarin may be increased.
Oral anticoagulants (warfarin)	Glutethimide	Inadequate therapeutic response to warfarin may occur.
Oral anticoagulants (warfarin)	Griseofulvin	The effects of warfarin may be decreased.
Oral anticoagulants (warfarin)	Histamine H_2 antagonists	The effects of warfarin may be increased.
Oral anticoagulants (warfarin)	Hydroxymethylglutaryl coenzyme A reductase inhibitors	The effects of warfarin may be increased.
Oral anticoagulants (warfarin)	Hydantoins	Hydantoin serum concentrations may be increased, resulting in possible toxicity. Prothrombin time may be increased, increasing the risk of bleeding.
Oral anticoagulants (warfarin)	Macrolides	The anticoagulant effect of warfarin may be increased.
Oral anticoagulants (warfarin)	Metronidazole	The effects of warfarin may be increased.
Oral anticoagulants (warfarin)	Nevirapine	The effects of warfarin may be decreased.
Oral anticoagulants (warfarin)	Penicillins	Large intravenous doses of penicillins can increase the bleeding risks of warfarin by prolonging bleeding time.
Oral anticoagulants (warfarin)	Quinidine derivatives	The effects of warfarin may be increased.
Oral anticoagulants (warfarin)	Quinolones	The effects of warfarin may be increased.
Oral anticoagulants (warfarin)	Rifamycins	The effects of warfarin may be decreased.
Oral anticoagulants (warfarin)	Sulfinpyrazone	The effects of warfarin may be increased.
Oral anticoagulants (warfarin)	Sulfonamides	The effects of warfarin may be increased.
Oral anticoagulants (warfarin)	Tamoxifen	The hypoprothrombinemic effect of warfarin is increased.
Oral anticoagulants	Tetracyclines	The effects of warfarin may be increased.

Generic Name	Interacting Medication or Disease	Potential Result
(warfarin)		
Oral anticoagulants (warfarin)	Thioamides	The effects of warfarin may be augmented.
Oral anticoagulants (warfarin)	Thiopurines	The effects of warfarin may be decreased.
Oral anticoagulants (warfarin)	Thyroid hormones	The effects of warfarin may be increased.
Oral anticoagulants (warfarin)	Tramadol	The effects of warfarin may be increased.
Oral anticoagulants (warfarin)	Trazodone	The hypoprothrombinemic effect of warfarin is decreased.
Oral anticoagulants (warfarin)	Vitamin E	The effects of warfarin may be increased.
Oral anticoagulants (warfarin)	Vitamin K	The effects of warfarin is attenuated or reversed, leading to possible thrombus formation.

Dosing and Administration

When converting patients from warfarin to apixaban or dabigatran etexilate mesylate, warfarin should be discontinued and apixaban or dabigatran etexilate mesylate should be started when the International Normalized Ratio (INR) is <2.0. When converting from warfarin, rivaroxaban should be started when the INR is <3.0. When switching between apixaban and anticoagulants other than warfarin, discontinue the treatment being taken and start the other treatment at the next scheduled dose. For patients currently receiving a parenteral anticoagulant, dabigatran etexilate mesylate or rivaroxaban should be started zero to two hours before the time that the next dose of the parenteral medication was to have been administered, or at the time of discontinuation of a continuously administered parenteral medication.[1-4,6,7]

Apixaban should be discontinued at least 48 hours prior to an elective surgery or invasive procedure that carries a moderate or high risk of unacceptable or clinically significant bleeding. For elective surgeries or invasive procedures with a low risk of bleeding or where the bleeding would be noncritical in location and easily controlled, discontinue apixaban at least 24 hours prior to the procedure. If possible, dabigatran etexilate mesylate should be discontinued one to five days before invasive or surgical procedures because of the increased risk of bleeding. A longer time should be considered for patients undergoing major surgery, spinal surgery, or placement of a spinal or epidural catheter or part, in whom complete hemostasis may be required. If surgery cannot be delayed, there is an increased risk of bleeding.[1] If anticoagulation must be discontinued to reduce the risk of bleeding with surgical or other procedures, rivaroxaban should be stopped at least 24 hours before the procedure. In deciding whether a procedure should be delayed until 24 hours after the last dose of rivaroxaban, the increased risk of bleeding should be weighed against the urgency of intervention. Rivaroxaban should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established. If oral medication cannot be taken after surgical intervention consider administering a parenteral anticoagulant.[1,6,7]

The recommended dose of rivaroxaban varies depending on indication. The recommended treatment duration for rivaroxaban is 35 and 12 days, respectively, for patients undergoing hip or knee replacement surgery. Rivaroxaban may be administered independently of meals when used for prophylaxis of deep vein thrombosis. When used in atrial fibrillation or the treatment and prevention of recurrence of deep vein thrombosis and pulmonary embolism, administration with the evening meal is recommended.[3,6,7]

The dosage and administration of warfarin must be individualized for each patient according to the patient's prothrombin time/INR response to the drug, with the dosage adjusted based on this measurement. The selected starting dose of warfarin should be based on the expected maintenance dose. The initial dose of warfarin is usually 2 to 5 mg/day; however, this dose should be modified based on consideration of patient-specific clinical factors. Lower initial doses should be considered for elderly

and/or debilitated patients. Regarding maintenance treatment, most patients are satisfactorily maintained at a dose of 2 to 10 mg/day. Flexibility of dosage is provided by breaking scored tablets in half, and the individual dose and interval should be gauged by the patient's prothrombin response. The duration of therapy in each patient is also individualized. In general, treatment with warfarin should be continued until the danger of thrombosis and embolism has passed.[4,6,7]

Table 16. Dosing and Administration[1-4,6,7]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Apixaban	Reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation: Tablet: 5 mg BID	Safety and efficacy in children have not been established.	Tablet: 2.5 mg 5 mg
Dabigatran etexilate mesylate	Reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation: Capsule: 150 mg BID	Safety and efficacy in children have not been established.	Capsule: 75 mg 150 mg
Rivaroxaban	Prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism in patients undergoing knee or hip replacement surgery: Tablet: 10 mg QD Reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation: Tablet: 20 mg QD Treatment of deep vein thrombosis and pulmonary embolism, and for the reduction in the risk of recurrence of deep vein thrombosis and of pulmonary embolism: Tablet: initial, 15 mg BID for the first 21 days; maintenance, 20 mg QD	Safety and efficacy in children have not been established.	Tablet: 10 mg 15 mg 20 mg
Warfarin	Prophylaxis and treatment of the thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement: Tablet: initial, 2 to 5 mg QD; maintenance, 2 to 10 mg QD; maintain an INR of 2.0 to 3.0 Prophylaxis and treatment of venous thrombosis and its extension, pulmonary embolism: Tablet: initial, 2 to 5 mg QD; maintenance, 2 to 10 mg QD; treat for six to 12 months or indefinitely Reduce the risk of death, recurrent myocardial infarction and thromboembolic events such as stroke or systemic embolization after myocardial infarction:	Safety and efficacy in children have not been established.*	Tablet: 1 mg 2 mg 2.5 mg 3 mg 4 mg 5 mg 6 mg 7.5 mg 10 mg

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	Tablet: initial, 2 to 5 mg QD; maintenance, 2 to 10 mg QD; maintain an INR of 3.0 to 4.0 (high intensity) or of 2.0 to 3.0 (moderate intensity)		

BID=twice-daily, INR=International Normalized Ratio, QD=once-daily

Clinical Guidelines

Table 17. Clinical Guidelines

Clinical Guideline	Recommendations
American College of Chest Physicians: **Antithrombotic Therapy and Prevention of Thrombosis, 9th edition (2012)**[23]	Management of anticoagulant therapy • For outpatients, vitamin K antagonist (VKA) therapy with warfarin 10 mg/day for the first two days, followed by dosing based on international normalized ratio (INR) measurements rather than starting with the estimated maintenance dose is suggested. • Routine use of pharmacogenetic testing for guiding doses of VKA therapy is not recommended. • For acute venous thromboembolism (VTE), it is suggested that VKA therapy be started on day one or two of low molecular weight heparin (LMWH) or low dose unfractionated heparin (UFH) therapy rather than waiting for several days to start. • For VKA therapy with stable INRs, INR testing frequency of up to 12 weeks is suggested rather than every four weeks. • For patients receiving previously stable VKA therapy who present with a single out-of-range INR ≤0.5 below or above therapeutic, it is suggested to continue the current dose and test the INR within one to two weeks. • For patients receiving stable VKA therapy presenting with a single subtherapeutic INR value, routine administering of bridging heparin is not recommended. • Routine use of vitamin K supplementation is suggested against with VKA therapy. • For patients receiving VKA therapy who are motivated and can demonstrate competency in self-management strategies, it is suggested that patient self-management be utilized rather than usual outpatient INR monitoring. • For maintenance VKA dosing, it is suggested that validated decision support tools be utilized rather than no decision support. • Concomitant use of nonsteroidal anti-inflammatory drugs and certain antibiotics should be avoided in patients receiving VKA therapy. • Concomitant use of platelet inhibitors should be avoided in patients receiving VKA therapy, except in situations where benefit is known or is highly likely to be greater than harm from bleeding. • With VKA therapy, a therapeutic INR range of 2.0 to 3.0 (target, 2.5) is recommended rather than a lower (<2.0) or higher (range, 3.0 to 5.0) range. • In patients with antiphospholipid syndrome with previous arterial or VTE, VKA therapy should be titrated to a moderate intensity INR (range, 2.0 to 3.0) rather than higher intensity (range, 3.0 to 4.5). • For discontinuations of VKA therapy, it is suggested that discontinuation be done abruptly rather than gradual tapering of the dose. • For initiation of intravenous (IV) UFH, the initial bolus and rate of continuous infusion should be weight adjusted or fixed-dose rather than

Clinical Guideline	Recommendations
	alternative regimens. • In outpatients with VTE receiving subcutaneous (SC) UFH, dosing should be weight-based without monitoring rather than fixed or weight-adjusted dosing with monitoring. • A reduction in therapeutic LMWH dose is suggested in patients with severe renal insufficiency rather than using standard doses. • In patients with VTE and body weight >100 kg, the treatment dose of fondaparinux should be increased from 7.5 to 10 mg/day SC. • For INRs between 4.5 and 10.0 with VKA therapy and no evidence of bleeding, routine use of vitamin K is not recommended. • For INRs >10.0 with VKA therapy and no evidence of bleeding, it is suggested that oral vitamin K be administered. • In patients initiating VKA therapy, routine use of clinical prediction rules for bleeding as the sole criterion to withhold VKA therapy is not recommended. • For VKA-associated major bleeding, rapid reversal of anticoagulation with four-factor prothrombin complex concentrate is suggested over plasma. Additional use of vitamin K 5 to 10 mg administered by slow IV injection is recommended rather than reversal with coagulation factors alone. <u>Prevention of VTE in nonsurgical patients</u> • Acutely ill hospitalized medical patients at increased risk of thrombosis: anticoagulant thromboprophylaxis with LMWH, low dose UFH (two or three times daily), or fondaparinux is recommended. Choice should be based on patient preference, compliance, and ease of administration, as well as on local factors affecting acquisition costs. • Acutely ill hospitalized patients at low risk of thrombosis: pharmacologic or mechanical prophylaxis is not recommended. • Acutely ill hospitalized medical patients who are bleeding or at high risk for bleeding: anticoagulant thromboprophylaxis is not recommended. • Acutely ill hospitalized medical patients at increased risk for thrombosis who are bleeding or at high risk of major bleeding: optimal use of mechanical thromboprophylaxis is suggested rather than no mechanical thromboprophylaxis. When bleeding risk decreases, and if VTE risk persists, it is suggested that pharmacologic thromboprophylaxis be substituted for mechanical thromboprophylaxis. • Acutely ill hospitalized medical patients who receive an initial course of thromboprophylaxis: extending the duration of thromboprophylaxis beyond the period of patient immobilization or acute hospital stay is suggested against. • Critically ill patients: routine ultrasound screening for deep vein thrombosis (DVT) is suggested against. • Critically ill patients: use of LMWH or low dose UFH thromboprophylaxis is suggested over no prophylaxis. • Critically ill patients who are bleeding or are at high risk for major bleeding: use of mechanical thromboprophylaxis until the bleeding risk decreases is suggested rather than no mechanical thromboprophylaxis. When bleeding risk decreases, pharmacologic thromboprophylaxis is suggested to be substituted for mechanical thromboprophylaxis. • Outpatients with cancer who have no additional risk factors for VTE: routine prophylaxis with LMWH or low dose UFH is suggested against, and prophylactic use of VKAs is not recommended.

Clinical Guideline	Recommendations
	• Outpatients with solid tumors who have additional risk factors for VTE with low risk of bleeding: prophylaxis with LMWH or low dose UFH is suggested over no prophylaxis. • Outpatients with cancer and indwelling central venous catheters: routine prophylaxis with LMWH or low dose UFH is suggested against, and prophylactic use of VKAs is suggested against. • Chronically immobilized patients residing at home or at a nursing home: routine thromboprophylaxis is suggested against. • Long distance travelers at increased risk of VTE: frequent ambulation, calf muscle exercise, or sitting in an aisle seat if feasible is suggested. • Long distance travelers at increased risk of VTE: use of properly fitted, below-knee graduated compression stockings during travel is suggested. For all other long distance travelers, use of graduated compression stockings is suggested against. • Long distance travelers: use of aspirin or anticoagulants to prevent VTE is suggested against. • Patients with asymptomatic thrombophilia: long term daily use of mechanical or pharmacologic thromboprophylaxis to prevent VTE is not recommended. <u>Prevention of VTE in nonorthopedic surgical patients</u> • General and abdominal-pelvic surgery patients at very low risk for VTE: no specific pharmacologic or mechanical prophylaxis is recommended for use other than early ambulation. • General and abdominal-pelvic surgery patients at low risk for VTE: mechanical prophylaxis is suggested over no prophylaxis. • General and abdominal-pelvic surgery patients at moderate risk for VTE who are not at high risk major bleeding complications: LMWH, low dose UFH, or mechanical prophylaxis is suggested over no prophylaxis. • General and abdominal-pelvic surgery patients at moderate risk for VTE who are at high risk for major bleeding complication or those in whom the consequences of bleeding are thought to be particularly severe: mechanical prophylaxis is suggested over no prophylaxis. • General and abdominal-pelvic surgery patients at high risk for VTE who are not at high risk for major bleeding complications: LMWH or low dose UFH is recommended over no prophylaxis. It is suggested that mechanical prophylaxis be added to pharmacologic prophylaxis. • High-VTE-risk patients undergoing abdominal or pelvic surgery for cancer who are not otherwise at high risk for major bleeding complications: extended duration (four weeks) of LMWH prophylaxis is recommended over limited duration prophylaxis. • High-VTE-risk general and abdominal-pelvic surgery patients who are at high risk for major bleeding complications or those in whom the consequences of bleeding are thought to be particularly severe: mechanical prophylaxis is suggested over no prophylaxis until the risk of bleeding diminishes and pharmacologic prophylaxis may be initiated. • General and abdominal-pelvic surgery patients at high risk for VTE in whom both LMWH and UFH are contraindicated or unavailable and who are not at high risk for major bleeding complications: low dose aspirin, fondaparinux, or mechanical prophylaxis is suggested over no prophylaxis. • General and abdominal-pelvic surgery patients: it is suggested that an

Clinical Guideline	Recommendations
	inferior vena cava filter not be used for primary VTE prevention. • General and abdominal-pelvic surgery patients: it is suggested that periodic surveillance with venous compression ultrasound not be performed. • Cardiac surgery patients with an uncomplicated postoperative course: mechanical prophylaxis is suggested over either no prophylaxis or pharmacologic prophylaxis. • Cardiac surgery patients whose hospital course is prolonged by one or more nonhemorrhagic surgical complications: adding pharmacologic prophylaxis with low dose UFH or LMWH to mechanical prophylaxis is suggested. • Thoracic surgery patients at moderate risk for VTE who are not at high risk for perioperative bleeding: low dose UFH, LMWH, or mechanical prophylaxis is suggested over no prophylaxis. • Thoracic surgery patients at high risk for VTE who are not at high risk for perioperative bleeding: low dose UFH or LWMH is suggested over no prophylaxis. It is suggested that mechanical prophylaxis be added to pharmacologic prophylaxis. • Thoracic surgery patients who are at high risk for major bleeding: mechanical prophylaxis over no prophylaxis is suggested until the risk of bleeding diminishes and pharmacologic prophylaxis may be initiated. • Craniotomy patients: mechanical prophylaxis is suggested over no prophylaxis or pharmacologic prophylaxis. • Craniotomy patients at very high risk for VTE: it is suggested that pharmacologic prophylaxis be added to mechanical prophylaxis once adequate hemostasis is established and the risk of bleeding decreases. • Patients undergoing spinal surgery: mechanical prophylaxis is suggested over no prophylaxis, UFH, or LMWH. • Patients undergoing spinal surgery at high risk of VTE: it is suggested that pharmacologic prophylaxis be added to mechanical prophylaxis once adequate hemostasis is established and the risk of bleeding decreases. • Major trauma patients: low dose UFH, LMWH, or mechanical prophylaxis is suggested over no prophylaxis. • Major trauma patients at high risk for VTE: it is suggested that mechanical prophylaxis be added to pharmacologic prophylaxis when not contraindicated by lower extremity injury. • Major trauma patients in whom LMWH and low dose UFH are contraindicated: mechanical prophylaxis is suggested over no prophylaxis when not contraindicated by lower extremity injury. It is suggested that either LMWH or low dose UFH be added when the risk of bleeding diminishes or the contraindication to heparin resolves. • Major trauma patients: it is suggested that an interior vena cava filter not be used for primary VTE prevention. • Major trauma patients: it is suggested that periodic surveillance with venous compression ultrasound not be performed. <u>Prevention of VTE in orthopedic surgery patients</u> • Total hip arthroplasty or total knee arthroplasty: use of one of the following for a minimum of 10 to 14 days rather than no antithrombotic prophylaxis is recommended: LMWH, fondaparinux, apixaban, dabigatran, rivaroxaban, low dose UFH, adjusted-dose VKA, aspirin, or an intermittent pneumatic compression device.

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	• Hip fracture surgery: use of one of the following for a minimum of 10 to 14 days rather than no antithrombotic prophylaxis is recommended: LMWH, fondaparinux, low dose UFH, adjusted-dose VKA, aspirin, or intermittent pneumatic compression device. • Patients undergoing major orthopedic surgery (total hip arthroplasty, total knee arthroplasty, hip fracture surgery) and receiving LMWH as thromboprophylaxis: it is recommended to start either 12 hours or more preoperatively or postoperatively rather than within four hours or less preoperatively or postoperatively. • Total hip or knee arthroplasty, irrespective of the concomitant use of an intermittent pneumatic compression device or length of treatment: LMWH is suggested in preference to other agents recommended as alternatives: fondaparinux, apixaban, dabigatran, rivaroxaban, low dose UFH, adjusted-dose VKA, or aspirin. • Hip replacement surgery, irrespective of the concomitant use of an intermittent pneumatic compression device or length of treatment: LMWH is suggested in preference to other agents recommended as alternatives: fondaparinux, low dose UFH, adjusted-dose VKA, or aspirin. • Major orthopedic surgery: it is suggested to extend thromboprophylaxis in the outpatient period for up to 35 days from the day of surgery rather than for only 10 to 14 days. • Major orthopedic surgery: it is suggested to use dual prophylaxis with an antithrombotic agent and an intermittent pneumatic compression device during the hospital stay. • Major orthopedic surgery in patients at an increased risk of bleeding: intermittent pneumatic compression device or no prophylaxis is suggested over pharmacologic prophylaxis. • Major orthopedic surgery in patients who decline or are uncooperative with injections or intermittent pneumatic compression device: apixaban or dabigatran etexilate mesylate (alternatively rivaroxaban or adjusted-dose VKA if apixaban or dabigatran etexilate mesylate are unavailable) is recommended over alternative forms of prophylaxis. • Major orthopedic surgery in patients with an increased bleeding risk or contraindications to both pharmacologic and mechanical prophylaxis: inferior vena cava filter placement for primary prevention of VTE is suggested against over no thromboprophylaxis. • Asymptomatic patients following major orthopedic surgery: doppler ultrasound screening before hospital discharge is not recommended. • Patients with lower leg injuries requiring leg immobilization: no prophylaxis is suggested rather than pharmacologic thromboprophylaxis. • Knee arthroscopy in patients without a history of prior VTE: no thromboprophylaxis is suggested rather than prophylaxis. <u>Antithrombotic therapy for VTE disease</u> • Acute DVT of the leg or pulmonary embolism (PE) treated with VKA therapy: initial treatment with parenteral anticoagulation (LMWH, fondaparinux, or IV or SC UFH) is recommended over no such initial treatment. • High clinical suspicion of acute VTE or PE: treatment with parenteral anticoagulation is suggested over no treatment while awaiting the results of diagnostic tests. • Intermediate clinical suspicion of acute VTE or PE: treatment with parenteral anticoagulation is suggested over no treatment if the results of

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	diagnostic tests are expected to be delayed for more than four hours. • Low clinical suspicion of acute VTE or PE: it is suggested to not treat with parenteral anticoagulants while awaiting the results of diagnostic tests, provided test results are expected within 24 hours. • Acute isolated distal DVT of the leg without severe symptoms or risk factors for extension: serial imaging of the deep veins for two weeks is suggested over initial anticoagulation. • Acute isolated distal DVT of the leg and severe symptoms or risk factors for extension: initial anticoagulation is suggested over serial imaging of the deep veins. • Acute isolated distal DVT of the leg in patients managed with initial anticoagulation: using the same approach as for patients with acute proximal DVT is recommended. • Acute isolated distal DVT of the leg who are managed with serial imaging: no anticoagulation if the thrombus does not extend is recommended; anticoagulation is suggested if the thrombus extends but remains confined to the distal veins; and anticoagulation is recommended if the thrombus extends into the proximal veins. • Acute DVT of the leg or PE: early initiation of VKA therapy is recommended over delayed initiation, and continuation of parenteral anticoagulation for a minimum on five days and until the INR is 2.0 or above for at least 24 hours. • Acute DVT of the leg or PE: LMWH or fondaparinux is suggested over IV or SC UFH. • Patients with acute DVT of the leg or PE receiving LMWH: once daily LMWH administration is suggested over twice daily administration. • Acute DVT of the leg and home circumstances are adequate: initial treatment at home is recommended over treatment in hospital. • Low risk PE and home circumstances are adequate: early discharge is suggested over standard discharge. • Acute proximal DVT of the leg: anticoagulation therapy alone is suggested over catheter-directed thrombolysis. • Acute proximal DVT of the leg: anticoagulation therapy alone is suggested over systemic thrombolysis. • Acute proximal DVT of the leg: anticoagulation therapy alone is suggested over venous thrombectomy. • Acute DVT of the leg in patients who undergo thrombosis removal: the same intensity and duration of anticoagulant therapy as in comparable patients who do not undergo thrombosis removal is recommended. • Acute DVT of the leg: use of an inferior vena cava filter in addition to anticoagulants is not recommended. • Acute proximal DVT of the leg in patients with contraindication to anticoagulation: use of an inferior vena cava filter is recommended. • Acute proximal DVT of the leg in patients with an inferior vena cava filter inserted as an alternative to anticoagulation: a conventional course of anticoagulant therapy is suggested if the risk of bleeding resolves. • Acute DVT of the leg: early ambulation is suggested over initial bed rest. • Acute VTE in patients receiving anticoagulant therapy: long term therapy is recommended over stopping anticoagulant therapy after about one week of initial therapy. • Acute symptomatic DVT of the leg: compression stockings are suggested. • Acute PE associated with hypotension in patients who do not have a high

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	bleeding risk: systemically administered thrombolytic therapy is suggested over no such therapy. • In most patients with acute PE not associated with hypotension: systemically administered thrombolytic therapy is not recommended. • In selected patients with acute PE not associated with hypotension and with a low bleeding risk who initial clinical presentation or clinical course after starting anticoagulant therapy, suggests a high risk of developing hypotension: administration of thrombolytic therapy is suggested. • Proximal DVT of the leg or PE provoked by surgery: treatment with anticoagulation for three months is recommended over treatment for a shorter period, treatment of a longer time limited period, or extended therapy. • Proximal DVT of the leg or PE provoked by a nonsurgical transient risk factor: treatment with anticoagulation for three months is recommended over treatment for a shorter period, treatment for a longer time limited period, extended therapy if there is high bleeding risk. Anticoagulation treatment for three months is suggested over extended therapy if there is a low or moderate bleeding risk. • Isolated distal DVT of the leg provoked by surgery or by a nonsurgical transient risk factor: treatment with anticoagulation for three months is suggested over treatment for a shorter period, and anticoagulation treatment for three months is recommended over treatment of longer time limited period or extended therapy. • Unprovoked DVT of the leg or PE: treatment with anticoagulation for three months is recommended over treatment of a shorter duration. After three months, patients should be evaluated for the risk-benefit ratio of extended therapy. • First VTE that is an unprovoked proximal DVT of the leg or PE in patients who have a low or moderate bleeding risk: extended anticoagulant therapy is suggested over three months of therapy. • First VTE that is an unprovoked proximal DVT of the leg or PE in patients who have a high bleeding risk: three months of anticoagulant therapy is recommended over extended therapy. • First VTE that is an unprovoked isolated distal DVT of the leg: three months of anticoagulation therapy is suggested over extended therapy in those with a low or moderate bleeding risk, and three months of anticoagulant treatment is recommended in those with a high bleeding risk. • Second unprovoked VTE or PE: extended anticoagulant therapy is recommended over three months of therapy in those who have a low bleeding risk, and extended anticoagulant therapy is suggested in patients with a moderate bleeding risk. • Second unprovoked VTE or PE in patients with a high bleeding risk: three months of anticoagulant therapy is suggested over extended therapy. • DVT of the leg or PE and active cancer: if the risk of bleeding is not high, extended anticoagulation therapy is recommended over three months of therapy, and if there is a high bleeding risk, extended anticoagulant therapy is suggested. • DVT of the leg or PE in patients treated with VKA: a therapeutic INR range of 2.0 to 3.0 (target, 2.5) is recommended over a lower (<2.0) or higher (range, 3.0 to 5.0) range for all treatment durations. • DVT of the leg or PE in patients with no cancer: VKA therapy is suggested over LMWH for long-term therapy. For patients with DVT or

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	PE and no cancer who are not treated with VKA therapy, LMWH is suggested over dabigatran etexilate mesylate or rivaroxaban for long term therapy. • DVT of the leg or PE and cancer: LMWH is suggested over VKA therapy. In patients with DVT of the leg or PE and cancer who are not treated with LMWH, VKA is suggested over dabigatran etexilate mesylate or rivaroxaban for long-term therapy. • DVT of the leg or PE in patients who receive extended therapy: treatment with the same anticoagulant chosen for the first three months is suggested. • Patients incidentally found to have asymptomatic DVT of the leg or PE: treatment with the same anticoagulant is suggested as for comparable patients with symptomatic DVT or PE. • In patients with chronic thromboembolic pulmonary hypertension, extended anticoagulation is recommended over stopping therapy. • Superficial vein thrombosis of the lower limb of at least 5 cm in length: use of a prophylactic dose of fondaparinux or LMWH for 45 days is suggested over no anticoagulation. • Superficial vein thrombosis in patients treated with anticoagulation: fondaparinux 2.5 mg/day is suggested over a prophylactic dose of LMWH. • Upper-extremity DVT that involves the axillary or more proximal veins: acute treatment with parenteral anticoagulation (LMWH, fondaparinux, or IV or SC UFH) over no such acute treatment. • Acute upper-extremity DVT that involves the axillary or more proximal veins: LMWH or fondaparinux is suggested over IV or SC UFH, and anticoagulation therapy alone is suggested over thrombolysis. • Upper-extremity DVT in patients undergoing thrombolysis: the same intensity and duration of anticoagulant therapy as in similar patients who do not undergo thrombolysis is recommended. • In most patients with upper-extremity DVT that is associated with a central venous catheter: it is suggested that the catheter not be removed if it is functional and there is an ongoing need for the catheter. • Upper-extremity DVT that involves the axillary or more proximal veins: a minimum duration of anticoagulation of three months is suggested over a shorter duration. • Upper-extremity DVT that is associated with a central venous catheter that is removed: three months of anticoagulation is recommended over a longer duration of therapy in patients with no cancer, and this is suggested in patients with cancer. • Upper-extremity DVT that is associated with a central venous catheter that is not removed: it is recommended that anticoagulation is continued as long as the central venous catheter remains over stopping after three months of treatment in patients with cancer, and this is suggested in patients with no cancer. • Upper-extremity DVT that is not associated with a central venous catheter or with cancer: three months of anticoagulation is recommended over a longer duration of therapy. • Acute symptomatic upper-extremity DVT: use of compression sleeves or venoactive medications is suggested against. • Symptomatic splanchnic vein thrombosis: anticoagulation is recommended over no anticoagulation.

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	• Symptomatic hepatic vein thrombosis: anticoagulation is suggested over no anticoagulation. • In patients with incidentally detected splanchnic vein thrombosis or hepatic vein thrombosis: no anticoagulation is suggested over anticoagulation. Antithrombotic therapy for atrial fibrillation (AF) • Patients with AF, including those with paroxysmal AF, who are at low risk of stroke: no therapy is suggested over antithrombotic therapy. For patients who choose antithrombotic therapy, aspirin is suggested over oral anticoagulation or combination therapy with aspirin and clopidogrel. • Patients with AF, including those with paroxysmal AF, who are at intermediate risk of stroke: oral anticoagulation is recommended over no therapy. Oral anticoagulation is suggested over aspirin or combination therapy with aspirin and clopidogrel. For patients who are unsuitable for or choose not to take an oral anticoagulant, combination therapy with aspirin and clopidogrel are suggested over aspirin. • Patients with AF, including those with paroxysmal AF, who are at high risk of stroke: oral anticoagulation is recommended over no therapy, aspirin, or combination therapy with aspirin and clopidogrel. For patients who are unsuitable for or choose not to take an oral anticoagulant, combination therapy with aspirin and clopidogrel is recommended over aspirin. • Patients with AF, including those with paroxysmal AF: for recommendations in favor of oral anticoagulation, dabigatran etexilate mesylate 150 mg twice daily is suggested over adjusted-dose VKA therapy (target INR range, 2.0 to 3.0). • Patients with AF and mitral stenosis: adjusted-dose VKA therapy is recommended over no therapy, aspirin, or combination therapy with aspirin and clopidogrel. For patients who are unsuitable for or choose not to take adjusted-dose VKA therapy, combination therapy with aspirin and clopidogrel is recommended over aspirin alone. • Patients with AF and stable coronary artery disease and who choose oral anticoagulation: adjusted-dose VKA therapy alone is suggested over the combination of adjusted-dose VKA therapy and aspirin. • Patients with AF at high risk of stroke during the first month after placement of a bare-metal stent or the first three to six months after placement of a drug-eluting stent: triple therapy (e.g., VKA therapy, aspirin, and clopidogrel) is suggested over dual antiplatelet therapy (e.g., aspirin and clopidogrel). After this initial period, a VKA plus a single antiplatelet agent is suggested over a VKA alone. At 12 months after stent placement, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease. • Patients with AF at intermediate risk of stroke during the first 12 months after placement of a stent: dual antiplatelet therapy is suggested over triple therapy. At 12 months after stent placement, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease. • Patients with AF at intermediate to high risk of stroke who experience an acute coronary syndrome (ACS) and do not undergo stent placement, for the first 12 months: adjusted-dose VKA therapy plus single antiplatelet therapy is suggested over dual antiplatelet therapy or triple therapy. After the first 12 months, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease. • Patients with AF at low risk of stroke: dual antiplatelet therapy is

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	suggested over adjusted-dose VKA therapy plus single antiplatelet therapy or triple therapy. After the first 12 months, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease. • Patients with AF being managed with a rhythm control strategy: it is suggested that antithrombotic therapy decisions follow the general risk-based recommendations for patients with nonrheumatic AF, regardless of the apparent persistence of normal sinus rhythm. • Patients with atrial flutter: it is suggested that antithrombotic therapy decisions follow the same risk-based recommendations as for AF. <u>Primary and secondary prevention of cardiovascular disease</u> • Patients ≥50 years of age without symptomatic cardiovascular disease: low dose aspirin (75 to 100 mg/day) is suggested over no aspirin therapy. • Patients with established coronary artery disease: long term single antiplatelet therapy with aspirin (75 to 100 mg/day) or clopidogrel (75 mg/day) is recommended over no antiplatelet therapy, and single antiplatelet therapy is suggested over dual antiplatelet therapy. • Patients in the first year after ACS who have not undergone percutaneous coronary intervention (PCI): dual antiplatelet therapy (ticagrelor 90 mg twice daily plus low dose aspirin 75 to 100 mg/day or clopidogrel 75 mg/day plus low dose aspirin 75 to 100 mg/day) is recommended over single antiplatelet therapy. Ticagrelor 90 mg twice daily plus low dose aspirin is suggested over clopidogrel 75 mg/day plus low dose aspirin. • Patients in the first year after an ACS who have undergone PCI with stent placement: dual antiplatelet therapy (ticagrelor 90 mg twice daily plus low dose aspirin 75 to 100 mg/day, clopidogrel 75 mg/day plus low dose aspirin, or prasugrel 10 mg/day plus low dose aspirin) is recommended over single antiplatelet therapy. Ticagrelor 90 mg twice daily plus low dose aspirin is suggested over clopidogrel 75 mg/day plus low dose aspirin. • Patients with anterior myocardial infarction (MI) and left ventricular thrombus, or at high risk for left ventricular thrombus, who do not undergo stenting: warfarin plus low dose aspirin (75 to 100 mg/day) is recommended over single antiplatelet therapy or dual antiplatelet therapy for the first three months. Thereafter, it is recommended that warfarin be discontinued and dual antiplatelet therapy should be continued for up to 12 months. After 12 months, single antiplatelet therapy is recommended as per the established coronary artery disease recommendations. • Patients with anterior MI and left ventricular thrombus, or at high risk for left ventricular thrombus, who undergo bare-metal stent placement: triple therapy (warfarin, low dose aspirin, clopidogrel 75 mg/day) for one month is suggested over dual antiplatelet therapy. Warfarin and single antiplatelet therapy for the second and third month post-bare-metal stent is suggested over alternative regimens and alternative time frames for warfarin use. Thereafter, it is recommended that warfarin be discontinued and dual antiplatelet therapy should be continued for up to 12 months. After 12 months, antiplatelet therapy is recommended as per the established coronary artery disease recommendations. • Patients with anterior MI and left ventricular thrombus, or at high risk for left ventricular thrombus who undergo drug-eluting stent placement: triple therapy (warfarin, low dose aspirin, clopidogrel 75 mg/day) for up to three to six months is suggested over alternative regimens and alternative durations of warfarin therapy. Thereafter, it is recommended that warfarin

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	be discontinued and dual antiplatelet therapy should be continued for up to 12 months. After 12 months, antiplatelet therapy is recommended as per the established coronary artery disease recommendations. • Patients who have undergone elective PCI with placement of bare-metal stent: dual antiplatelet therapy with aspirin 75 to 325 mg/day and clopidogrel 75 mg/day for one month is recommended over single antiplatelet therapy. For the subsequent 11 months, dual antiplatelet therapy with combination low dose aspirin 75 to 100 mg/day and clopidogrel 75 mg/day is suggested over single antiplatelet therapy. After 12 months, single antiplatelet therapy is recommended over continuation of dual antiplatelet therapy. • Patients who have undergone elective PCI with placement of drug-eluting stent: dual antiplatelet therapy with aspirin 75 to 325 mg/day and clopidogrel 75 mg/day for three to six months is recommended over single antiplatelet therapy. After three to six months, continuation of dual antiplatelet therapy with low dose aspirin 75 to 100 mg/day and clopidogrel 75 mg/day is suggested to be continued until 12 months over antiplatelet therapy. After 12 months, single antiplatelet therapy is recommended over continuation of dual antiplatelet therapy. Single antiplatelet therapy thereafter is recommended as per the established coronary artery disease recommendations. • Patients who have undergone elective bare-metal stent or drug-eluting stent placement: low dose aspirin 75 to 100 mg/day and clopidogrel 75 mg/day is recommended over cilostazol in addition to these drugs. Aspirin 75 to 100 mg/day or clopidogrel 75 mg/day as part of dual antiplatelet therapy is suggested over the use of either drug with cilostazol. Cilostazol 100 mg twice daily as a substitute for either low dose aspirin or clopidogrel as part of a dual antiplatelet regimen in patients with an allergy or intolerance of either drug class is suggested. • Patients with coronary artery disease undergoing elective PCI but no stent placement: for the first month dual antiplatelet therapy with aspirin 75 to 325 mg/day and clopidogrel 75 mg/day is suggested over single antiplatelet therapy. Single antiplatelet therapy thereafter is recommended as per the established coronary artery disease recommendations. • Patients with systolic left ventricular dysfunction without established coronary artery disease and no left ventricular thrombus: it is suggested that antiplatelet therapy and warfarin not be used. • Patients with systolic left ventricular dysfunction without established coronary artery disease with identified acute left thrombus: moderate intensity warfarin for at least three months is suggested. • Patients with systolic left ventricular dysfunction and established coronary artery disease: recommendations are as per the established coronary artery disease recommendations.
American Heart Association/American Stroke Association: **Oral Antithrombotic Agents for the Prevention of Stroke in Nonvalvular Atrial Fibrillation: A Science Advisory for**	<u>Prevention of stroke in nonvalvular AF</u> • Apixaban, dabigatran etexilate mesylate, rivaroxaban and warfarin are all indicated for the prevention of first and recurrent stroke in patients with nonvalvular AF. • 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 the patient has been taking warfarin. • Dabigatran etexilate mesylate 150 mg twice daily is an efficacious al-

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Healthcare Professionals (2012)[33]	ternative to warfarin for the prevention of first and recurrent stroke in patients with nonvalvular AF who have at least one additional risk factor and a creatinine clearance (CrCl) >30 mL/min. • The use of dabigatran etexilate mesylate 75 mg twice daily in patients with AF and at least one additional risk factor who have a low CrCl (15 to 30 mL/min) may be considered, but its safety and efficacy have not been established. The use of dabigatran etexilate mesylate in patients with more severe renal failure is not recommended in patients with a CrCl <15 mL/min. • Apixaban 5 mg twice daily is an effective alternative to aspirin in patients with nonvalvular AF deemed unsuitable for VKA therapy with one or more additional risk factor and no more than one of the following characteristics: age ≥80 years, weight ≤60 kg or serum creatinine ≥1.5 mg/dL. • Although safety and efficacy have not been established, apixaban 2.5 mg twice daily may be considered as an alternative to aspirin in patients with nonvalvular AF deemed unsuitable for VKA therapy who have one or more additional risk factor and two or more of the following criteria: age ≥80 years, weight ≤60 kg or serum creatinine ≥1.5 mg/dL. • Apixaban 5 mg twice daily is a relatively safe and efficacious alternative to warfarin in patients with nonvalvular AF deemed appropriate for VKA therapy that have one or more risk factors and no more than one of the following: age ≥80 years, weight ≤60 kg, or serum creatinine ≥1.5 mg/dL. • Apixaban should not be used if the CrCl is <25 mL/min. • In patients with nonvalvular AF who are at moderate to high risk of stroke (prior history of transient ischemic attack [TIA], stroke, or systemic embolization or have two additional risk factors), rivaroxaban 20 mg daily is a reasonable alternative to warfarin. • In patients with renal impairment and nonvalvular AF who are at moderate to high risk of stroke (prior history of TIA, stroke, or systemic embolization or two or more additional risk factors), with a CrCl 15 to 50 mL/min, rivaroxaban 15 mg daily may be considered; however, its safety and efficacy have not been established. • Rivaroxaban should not be used if the CrCl is <15 mL/min. • The safety and efficacy of combining dabigatran, rivaroxaban, or apixaban with an antiplatelet agent have not been established.
American College of Cardiology Foundation/American Heart Association/ Heart Rhythm Society: **Focused Update on the Management of Patients with Atrial Fibrillation (Updating the 2006 Guideline) (2011)**[9]	• With the exception of the recommendations presented in this Focused Update, the full-text guideline remains current. The 2006 guidelines are outlined below.[10] <u>Recommendations for combining anticoagulant with antiplatelet therapy</u> • Multiple trials have demonstrated that oral anticoagulation with warfarin is effective for the prevention of thromboembolism in AF patients. • Aspirin only offers modest protection against stroke in AF patients. • Adjusted-dose oral anticoagulation is more efficacious than aspirin for prevention of stroke in patients with AF. • The addition of clopidogrel to aspirin to reduce the risk of major vascular events, including stroke, might be considered in patients with AF in whom oral anticoagulation with warfarin is considered unsuitable due to patient preference or the physician's assessment of the patient's ability to safely sustain anticoagulation.

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American College of Cardiology Foundation/ American Heart Association/Heart Rhythm Society: **Focused Update on the Management of Patients with Atrial Fibrillation (Update on Dabigatran) (2011)**[24]	Recommendations for emerging antithrombotic agents • Dabigatran etexilate mesylate is useful as an alternative to warfarin for the prevention of stroke and systemic thromboembolism in patients with paroxysmal to permanent AF and risk factors for stroke or systemic embolization who do not have a prosthetic heart valve or hemodynamically significant valve disease, severe renal failure (CrCl <15 mL/min), or advanced liver disease. • Because of the twice-daily dosing and greater risk of nonhemorrhagic side effects with dabigatran, patients already taking warfarin with excellent INR control may have little to no gain by switching to dabigatran. • Selection of patients with AF, who have at least one additional risk factor for stroke, who could benefit from dabigatran etexilate mesylate over warfarin should consider individual clinical features including the ability to comply with twice-daily dosing, availability of an anticoagulation management program to sustain routine monitoring of INR, patient preferences, cost and other factors.
American College of Cardiology/ American Heart Association/ European Society of Cardiology: **Guidelines for the Management of Patients with Atrial Fibrillation (Executive Summary, 2006)**[10]	Preventing thromboembolism • Antithrombotic therapy to prevent thromboembolism is recommended for all patients with AF, except those with lone AF or contraindications. • Selection of antithrombotic therapy should be based upon absolute risks of stroke and bleeding and the relative risk and benefit for a given patient. For patients without mechanical heart valves at high risk of stroke, chronic oral anticoagulation therapy with a VKA is recommended in a dose adjusted to achieve an INR of 2.0 to 3.0, unless contraindicated. Factors associated with highest risk for stroke in patients with AF are prior thromboembolism (e.g., stroke, TIA, systemic embolism) and rheumatic mitral stenosis. • Anticoagulation with a VKA is recommended for patients with more than one moderate risk factor. Such factors include age ≥75, hypertension, heart failure, impaired left ventricular systolic function (ejection fraction ≤35% or fractional shortening <25%) and diabetes. • INR should be determined at least weekly during initiation of therapy and monthly when anticoagulation is stable. • Aspirin (81 to 325 mg/day) is recommended as an alternative to VKA in low-risk patients or in those with contraindications to oral anticoagulation. • For patients with AF who have mechanical heart valves, the target intensity of anticoagulation should be based on the type of prosthesis, maintaining an INR ≥2.5. • Antithrombotic therapy is recommended for patients with atrial flutter as for those with AF. • For primary prevention of thromboembolism in patients with nonvalvular AF who have just one validated risk factor (age ≥75 [especially in female patients], hypertension, heart failure, impaired left ventricular function, diabetes) antithrombotic therapy with either aspirin or a VKA is reasonable, based upon an assessment of the risk of bleeding complications, ability to safely sustain adjusted chronic anticoagulation and patient preferences. • For patients with nonvalvular AF who have one or more of the less well validated risk factors (age 65 to 74 years, female gender, coronary artery disease), antithrombotic therapy with either aspirin or a VKA is reasonable for prevention of thromboembolism. The choice of agent should be based upon the risk of bleeding complications, ability to safely

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	sustain adjusted chronic anticoagulation, and patient preferences. • It is reasonable to select antithrombotic therapy using the same criteria irrespective of the pattern (i.e., paroxysmal, persistent, permanent) of AF. • In patients with AF who do not have mechanical prosthetic heart valves, it is reasonable to interrupt anticoagulation for up to one week without substituting heparin for surgical or diagnostic procedures that carry a risk of bleeding. • It is reasonable to reevaluate the need for anticoagulation at regular intervals. • In patients ≥75 years at increased risk of bleeding but without frank contraindications to oral anticoagulant therapy, and in other patients with moderate risk factors for thromboembolism who are unable to safely tolerate anticoagulation at the standard intensity of INR 2.0 to 3.0, a lower INR target of 2.0 (range, 1.6 to 2.5) may be considered for primary prevention of ischemic stroke and systemic embolism. • When surgical procedures require interruption of oral anticoagulant therapy for longer than one week in high-risk patients, UFH may be administered or LMWH given by SC injection, although the efficacy of these alternatives in this situation is uncertain. • Following PCI or revascularization surgery in patients with AF, low-dose aspirin (<100 mg/day) and/or clopidogrel (75 mg/day) may be given concurrently with anticoagulation to prevent myocardial ischemic events. These strategies have not been thoroughly evaluated and are associated with an increased risk of bleeding. • In patients undergoing PCI, anticoagulation may be interrupted to prevent bleeding at the site of peripheral arterial puncture, but the VKA should be resumed as soon as possible after the procedure and the dose adjusted to achieve an INR in the therapeutic range. Aspirin may be given temporarily during the hiatus, but the maintenance regimen should then consist of the combination of clopidogrel (75 mg/day) plus warfarin (INR, 2.0 to 3.0). Clopidogrel should be given for a minimum of one month after implantation for a bare metal stent, at least three months for a sirolimus-eluting stent, at least six months for paclitaxel-eluting stent, and 12 months or longer in selected patients, following which warfarin may be continued as monotherapy in the absence of a subsequent coronary event. When warfarin is given in combination with clopidogrel or low dose aspirin, the dose intensity must be carefully regulated. • In patients with AF <60 years without heart disease or risk factors for thromboembolism (lone AF), the risk of thromboembolism is low without treatment and the effectiveness of aspirin for primary prevention of stroke relative to the risk of bleeding has not been established. • In patients with AF who sustain ischemic stroke or systemic embolism during treatment with low intensity anticoagulation (INR, 2.0 to 3.0), rather than add an antiplatelet agent, it may be reasonable to raise the intensity of the anticoagulation to a maximum target INR of 3.0 to 3.5. • Long-term anticoagulation with a VKA is not recommended for primary prevention of stroke in patients <60 years without heart disease (lone AF) or any risk factors for thromboembolism.
The American Heart Association: **Management of Massive and Submassive**	<u>Recommendations for initial anticoagulation for acute PE</u> • Therapeutic anticoagulation with SC LMWH, IV or SC UFH with monitoring, unmonitored weight-based SC UFH, or SC fondaparinux should be given to patients with objectively confirmed PE and no contraindications to anticoagulation.

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Pulmonary Embolism, Iliofemoral Deep Vein Thrombosis, and Chronic Thromboembolic Pulmonary Hypertension: A Scientific Statement From the American Heart Association (2011)[27]	• Therapeutic anticoagulation during the diagnostic workup should be given to patients with intermediate or high clinical probability of PE and no contraindications to anticoagulation. Fibrinolysis is not recommended for undifferentiated cardiac arrest. Recommendations for initial anticoagulation for patients with iliofemoral DVT • In the absence of suspected or proven heparin induced thrombocytopenia, patients with iliofemoral DVT should receive therapeutic anticoagulation with IV UFH, SC UFH, a LMWH agent, or fondaparinux. • Patients with iliofemoral DVT who have suspected or proven heparin-induced thrombocytopenia should receive a direct thrombin inhibitor. Recommendations for long-term anticoagulation therapy for patients with iliofemoral DVT • Adult patients with iliofemoral DVT who receive oral warfarin as first-line long-term anticoagulation therapy should have warfarin overlapped with initial anticoagulation therapy for a minimum of five days and until the INR is >2.0 for at least 24 hours, and then targeted to an INR 2.0 to 3.0. • Patients with first episode iliofemoral DVT related to a major reversible risk factor should have anticoagulation stopped after three months. • Patients with recurrent or unprovoked iliofemoral DVT should have at least six months of anticoagulation and be considered for indefinite anticoagulation with periodic reassessment of the risks and benefits of continued anticoagulation. • Cancer patients with iliofemoral DVT should receive LMWH monotherapy for at least three to six months, or as long as the cancer or its treatment (e.g., chemotherapy) is ongoing. • In children with DVT, the use of LMWH monotherapy may be reasonable.
American College of Cardiology/American Heart Association and American College of Cardiology/American Heart Association: **Guideline for the Management of Patients with ST-Segment Elevation Myocardial Infarction (2013)**[25]	Complications after ST-elevation MI (STEMI): anticoagulation • Anticoagulant therapy with a VKA should be provided to patients with ST-elevation myocardial infarction and AF with $CHADS_2$ score of two or more, mechanical heart valves, VTE, or hypercoagulable disorder. • The duration of triple-antithrombotic therapy with a VKA, aspirin, and a $P2Y_{12}$ receptor inhibitor should be minimized to the extent possible to limit the risk of bleeding. • Anticoagulant therapy with a VKA is reasonable for patients with STEMI and asymptomatic left ventricle mural thrombi. • Anticoagulant therapy may be considered for patients with STEMI and anterior apical akinesis or dyskinesis. • Targeting VKA therapy to a lower INR (e.g., 2.0 to 2.5) might be considered in patients with STEMI who are receiving dual antiplatelet therapy.
American College of Cardiology/American Heart Association: **2012 Focused Update Replacing the 2011 Focused Update and Updating the 2007 Guidelines for the Management of Patients with**	Recommendations for warfarin therapy • Use of warfarin in conjunction with aspirin and/or a $P2Y_{12}$ receptor inhibitor is associated with an increased risk of bleeding, and patients and clinicians should watch for bleeding, especially gastrointestinal, and seek medical evaluation for evidence of bleeding. • Warfarin with or without low-dose aspirin (75 to 81 mg/day; INR, 2.0 to 2.5) may be reasonable for patients at high coronary artery disease risk and low bleeding risk who do not require or are intolerant of a $P2Y_{12}$ receptor inhibitor.

Clinical Guideline	Recommendations
Unstable Angina/ Non-ST-Elevation Myocardial Infarction (2012)[28]	• Targeting an oral anticoagulant therapy to lower INR (e.g., 2.0 to 2.5) might be reasonable in patients with unstable angina/non-ST-elevation myocardial infarction managed with aspirin and a $P2Y_{12}$ receptor inhibitor.
European Society of Cardiology: **Guidelines for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation (2011)**[29]	• These guidelines provide no formal recommendations for the use of oral anticoagulants.
American College of Cardiology/American Heart Association: **2007 Chronic Angina Focused Update of the 2002 Guidelines for the Management of Patients With Chronic Stable Angina (2007)**[30]	• Aspirin should be started at 75 to 162 mg/day and continued indefinitely in all patients unless contraindicated. • The use of warfarin in conjunction with aspirin and/or clopidogrel is associated with an increased risk of bleeding and should be monitored closely.
The American College of Cardiology/ American Heart Association: **Practice Guidelines for the Management of Patients with Peripheral Artery Disease (2011)**[31]	<u>Exercise and lower extremity peripheral artery disease (PAD) rehabilitation</u> • A program of supervised exercise training is recommended as an initial treatment modality for patients with intermittent claudication. • Supervised exercise training should be performed for a minimum of 30 to 45 minutes, in sessions performed at least three times/week for a minimum of 12 weeks. • The usefulness of unsupervised exercise programs is not well established as an effective initial treatment modality for patients with intermittent claudication. <u>Smoking cessation</u> • Patients who are smokers or former smokers should be asked about status of tobacco use at every visit. Patients with lower extremity PAD who use tobacco should be advised to stop smoking. • Patients should be provided with counseling and assistance with developing a plan for smoking cessation. • One or more of the following pharmacological therapies should be offered if not contraindicated: varenicline, bupropion and nicotine replacement therapy. <u>Antiplatelet and antithrombotic drugs</u> • Antiplatelet therapy is indicated to reduce the risk of MI, stroke and vascular death in patients with symptomatic atherosclerotic lower extremity PAD and in asymptomatic patients with ankle brachial index ≤0.90. The usefulness of antiplatelet therapy is not well established in asymptomatic patients with ankle brachial index between 0.91 and 0.99. • Aspirin (75 to 325 mg/day) is recommended to reduce the risk of cardiovascular events. Clopidogrel (75 mg/day) is recommended as an alternative to aspirin.

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	• Combination of aspirin and clopidogrel may be considered to reduce the risk of cardiovascular events in patients with symptomatic atherosclerotic lower extremity PAD who are at high cardiovascular risk and not at increased risk of bleeding. • The addition of warfarin to antiplatelet therapy is of no proven benefit and is potentially harmful due to increased risk of major bleeding. <u>Medical and pharmacological treatment for claudication</u> • Cilostazol (100 mg orally twice daily) is indicated as an effective therapy to improve symptoms and increase walking distance in patients with lower extremity PAD and intermittent claudication (in the absence of heart failure). • A therapeutic trial of cilostazol should be considered in all patients with lifestyle-limiting claudication (in the absence of heart failure). • Pentoxifylline (400 mg three times daily) may be considered as second-line alternative therapy to cilostazol to improve walking distance in patients with intermittent claudication. • The clinical effectiveness of pentoxifylline as therapy for intermittent claudication is marginal and not well established. • The effectiveness of L-arginine for patients with intermittent claudication is not well established. • The effectiveness of propionyl L-carnitine as a therapy to improve walking distance in patients with intermittent claudication is not well established. • The effectiveness of ginkgo biloba as a therapy to improve walking distance in patients with intermittent claudication is not well established. • Oral vasodilator prostaglandins such as beraprost* and iloprost are not effective medications to improve walking distance in patients with intermittent claudication. • Vitamin E is not recommended as a treatment for patients with intermittent claudication. • Chelation (e.g. ethylenediaminetetraacetic acid) is not indicated for treatment of intermittent claudication and may have harmful adverse effects.

American Heart Association/American Stroke Association: **Guidelines for the Prevention of Stroke in Patients with Stroke or Transient Ischemic Attack (2010)**[32]	<u>Recommendations for patients with cardioembolic stroke types</u>
	• AF:
	  o For patients with ischemic stroke or TIA with paroxysmal or permanent AF, anticoagulation with a VKA (target INR, 2.0 to 3.0) is recommended.
	  o For patients unable to take oral anticoagulants, aspirin alone is recommended.
	  o The combination of clopidogrel plus aspirin carries a risk of bleeding similar to that of warfarin and therefore is not recommended for patients with a hemorrhagic contraindication to warfarin.
	  o For patients with AF at high risk for stroke who require temporary interruption of oral anticoagulation, bridging therapy with a LMWH agent administered SC is reasonable.
	• Acute MI and left ventricular thrombus:
	  o Patients with ischemic stroke or TIA in the setting of an acute MI complicated by left ventricular mural thrombus formation should be treated with oral anticoagulation (target INR, 2.5; range, 2.0 to 3.0) for at least three months.

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	• Cardiomyopathy: o In patients with prior stroke or transient cerebral ischemic attack in sinus rhythm who have cardiomyopathy characterized by systolic dysfunction, the benefit of warfarin has not been established. o Warfarin (INR, 2.0 to 3.0), aspirin (81 mg/day), clopidogrel (75 mg/day), or the combination of aspirin (25 mg twice-daily) plus extended-release dipyridamole (200 mg twice-daily) may be considered to prevent recurrent ischemic events in patients with pervious ischemic stroke or TIA and cardiomyopathy. • Native valvular heart disease: o For patients with ischemic stroke or TIA who have rheumatic mitral valve disease, whether or not AF is present, long-term warfarin therapy is reasonable with an INR target range of 2.5 (range, 2.0 to 3.0). o To avoid additional bleeding risk, antiplatelet agents should not be routinely added to warfarin. o For patients with ischemic stroke or TIA and native aortic or nonrheumatic mitral valve disease who do not have AF, antiplatelet therapy may be reasonable. o For patients with ischemic stroke or TIA and mitral annular calcification, antiplatelet therapy may be considered. o For patients with mitral valve prolapse who have ischemic stroke or TIA, long-term antiplatelet therapy may be considered. • Prosthetic heart valves: o For patients with ischemic stroke or TIA who have mechanical prosthetic heart valves, warfarin is recommended with a target INR of 3.0 (range, 2.5 to 3.5). o For patients with prosthetic heart valves who have an ischemic stroke or systemic embolism despite adequate therapy with oral anticoagulants, aspirin 75 to 100 mg/day in addition to oral anticoagulants and maintenance of the INR at a target of 3.0 (range, 2.5 to 3.5) is reasonable if the patient is not at high risk of bleeding. o For patients with ischemic stroke or TIA who have bioprosthetic heart valves with no other source of thromboembolism, anticoagulation with warfarin (INR, 2.0 to 3.0) may be considered.

*Agent not available in the United States.

Conclusions

The oral anticoagulants consist of apixaban (Eliquis®), dabigatran etexilate mesylate (Pradaxa®), rivaroxaban (Xarelto®) and warfarin (Coumadin®, Jantoven®). Apixaban, dabigatran etexilate mesylate and rivaroxaban are Food and Drug Administration (FDA)-approved to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF).[1-3] Rivaroxaban is also approved for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery and for the treatment and reduction in the risk of recurrence of DVT and PE.[3] Warfarin has various indications, including prophylaxis and/or treatment of PE; prophylaxis and/or treatment of thromboembolic complications associated with AF and/or cardiac valve replacement prophylaxis and/or treatment of venous thrombosis and its extension; and reduce the risk of death, recurrent myocardial infarction (MI) and thromboembolic events such as stroke or systemic embolization after MI.[4] Warfarin, along with aspirin, has been the principle oral anticoagulant for the past 60 years in high-risk AF patients.[5] Warfarin is a generically available vitamin K antagonist (VKA), and the evidence from clinical trials and recommendations from current clinical guidelines support the use of

warfarin in FDA-approved indications.[9-10,23-33] Warfarin and rivaroxaban are approved for once-daily dosing, while apixaban and dabigatran etexilate mesylate are administered twice-daily. Apixaban, dabigatran etexilate mesylate and rivaroxaban require a dose adjustment in patients with renal impairment and are only available as branded products. Furthermore, 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.[1-4]

The available oral anticoagulants have different mechanisms of action and affect different parts of the coagulation cascade.[1-4] Dabigatran etexilate mesylate is a direct thrombin inhibitor that prevents conversion of fibrinogen into fibrin, while apixaban and rivaroxaban selectively block the active site of factor Xa, preventing the production of thrombin and ultimately preventing platelet activation and the formation of fibrin clots.[1-3] The major advancement with apixaban, dabigatran etexilate mesylate and rivaroxaban is that they do not require the routine monitoring required with warfarin therapy; however, it may be difficult for physicians to objectively assess adherence to therapy. Moreover, apixaban, dabigatran etexilate mesylate and rivaroxaban are not associated with the food and drug interactions that are associated with warfarin.

In a large head-to-head trial, apixaban was superior to warfarin in preventing stroke or systemic embolism, with less major bleeding and intracranial bleeding compared to warfarin, and a similar incidence of gastrointestinal bleeding. Notably, apixaban also reduced death from any cause compared to warfarin.[13] Dabigatran etexilate mesylate demonstrated non inferiority for reducing the risk of stroke and systemic embolism, with a dose of 150 mg twice-daily achieving “superiority” over warfarin. In this trial, the incidence of major bleeding was also reduced with dabigatran etexilate mesylate compared to warfarin. In general, evidence suggests that the two agents are comparable in terms of overall bleeding, with more intracranial bleeding being associated with warfarin and more gastrointestinal bleeding being associated with dabigatran etexilate mesylate.[15] Rivaroxaban was compared to warfarin in a large, double-blind trial including over 14,000 patients at risk for stroke. Rivaroxaban demonstrated non inferiority to warfarin in regard to the primary endpoint, a composite of stroke or systemic embolism; however, “superiority” compared to warfarin was not achieved. The incidence of major and clinically relevant nonmajor bleeding between rivaroxaban and warfarin was similar. The rate of intracranial bleeding was significantly lower with rivaroxaban compared to warfarin, but major bleeding from a gastrointestinal site was more common with rivaroxaban.[16] For the prophylaxis of DVT, rivaroxaban was evaluated in four trials compared to enoxaparin, a low molecular weight heparin agent (LMWH), for use as thromboprophylaxis in patients undergoing hip and knee replacement surgeries. 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. In addition, there were similar rates of major bleeding and hemorrhagic wound complications between rivaroxaban and enoxaparin. These trials evaluated both short (10 to 14 days) and extended (31 to 30 days) thromboprophylaxis with rivaroxaban.[17-20] In patients with an acute, symptomatic, proximal DVT without symptomatic PE, and acute, symptomatic PE with or without symptomatic DVT, treatment with rivaroxaban was associated with a reduction in symptomatic, recurrent VTE (composite of DVT or nonfatal or fatal PE) compared to standard therapy, without an increase in bleeding events.[21,22]

In 2011, the American College of Cardiology released a focused update on the management of AF stating that dabigatran etexilate mesylate is useful as an alternative to warfarin, and patients already receiving warfarin with excellent International Normalized Ratio (INR) control may have little to gain by switching to dabigatran etexilate mesylate.[24] Since then, the 2012 American College of Chest Physicians guidelines regarding antithrombotic therapy and prevention of thrombosis, state that oral anticoagulation is recommended in patients with AF at intermediate to high risk of stroke, with dabigatran etexilate mesylate suggested over adjusted-dose VKA therapy.[23] Neither organization provides guidance as to the role of apixaban or rivaroxaban in the management of AF.[9,10,23,24] A recent Science Advisory by the American Heart Association and American Stroke Association states that apixaban, dabigatran etexilate mesylate and rivaroxaban are recommended as alternatives to warfarin in patients with AF who have at least one additional risk factor for stroke.[33] All of the oral anticoagulants are recommended as potential options for thromboprophylaxis of total hip and knee arthroplasty, with LMWH suggested in preference to other

recommended options. In general, recommendations from other guidelines are in line with the American College of Chest Physicians.

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