Overview of Novel Oral Anticoagulants
Including a Review of Efficacy and Safety in Atrial Fibrillation

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Background

Historically, agents for anticoagulation have been limited to warfarin, a vitamin K antagonist (VKA), and parenteral drugs such as low molecular weight heparin (LMWH) and unfractionated heparin (UFH).[1] Of late, several oral anticoagulant drugs have emerged, including dabigatran, rivaroxaban, apixaban, and, most recently, edoxaban.[2-5] A summary of their indications and dosing information may be seen in Table 1.[2-6]

All of the anticoagulant drugs outlined in Table 1 are approved by the Food and Drug Administration (FDA) for the prevention or reduction in risk of stroke and systemic embolism in patients with atrial fibrillation, as well as treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE).[2-6] With regard to treatment of DVT and PE, initiation of dabigatran and edoxaban must be preceded by 5-10 days of parenteral anticoagulant therapy.[3,4] In contrast, parenteral anticoagulation is not required before initiation of apixaban or rivaroxaban,[2,5] and warfarin initiation should overlap with parenteral anticoagulation.[6] In addition to these indications, apixaban, dabigatran, and rivaroxaban are approved for DVT prevention in patients undergoing hip or knee replacement surgery (hip only for dabigatran).[2,3,5]

Place in therapy

The place in therapy for the new oral anticoagulant drugs is unclear and varies per indication. The use of novel agents has been addressed by the American College of Chest Physicians (ACCP) in their (February) 2012 guidelines on antithrombotic therapy and prevention of thrombosis,[1,7-10] and in their 2016 update on treatment of venous thromboembolic (VTE) disease.[11] As of February 2012, dabigatran and rivaroxaban had received FDA approval for reduction in risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation and DVT prophylaxis in patients undergoing hip or knee surgery, respectively.[12] Apixaban and edoxaban were in development; apixaban was approved in December 2012 and edoxaban was approved in January 2015. A summary of the ACCP recommendations may be seen in Table 2. Based on the 2012 recommendations, it appears that use of the novel oral anticoagulants is generally not preferred, with the exception of secondary prevention of stroke, for which dabigatran is recommended over VKA therapy.[1,7-10] However, in the 2016 recommendations on VTE treatment, ACCP states that all 4 novel oral anticoagulants are preferred to warfarin for treatment of DVT of the leg or PE in patients without cancer.[11] They also provide consideration factors for choice of initial and long-term treatment of VTE (listed in Table 3). Importantly, the ACCP notes that their guidelines on other topics (e.g., prevention of VTE in surgical or nonsurgical patients, prevention and antithrombotic therapy for ischemic stroke) are being updated.

Comparative efficacy in patients with atrial fibrillation

There are several meta-analyses evaluating the comparative efficacy of the novel oral anticoagulants and warfarin.[13] The majority of these focus on 3 phase 3 trials: RE-LY, ROCKET AF, and ARISTOTLE.[14-16] Additional phase 3 trials involving subjects with atrial fibrillation include J-ROCKET AF and ENGAGE AF-TIMI.[17,18] These trials are outlined in Table 4.[14-22] All of these studies were designed primarily to evaluate non-inferiority of the novel oral anticoagulant to warfarin.[14-18] ROCKET AF, ARISTOTLE, and ENGAGE-AF TIMI included secondary analyses for superiority.[15,16,18] Compared to warfarin, dabigatran (150 mg twice daily) was found to be non-inferior in reduction of stroke and systemic embolism.[14] Rivaroxaban[15,17] and edoxaban (at both high and low doses)[18] were also found to be non-inferior to warfarin in the prevention of stroke or systemic embolism. The investigators of ARISTOTLE determined that apixaban was not only non-inferior but superior to warfarin for prevention of stroke and systemic embolism in their study.[16]

Cope et al performed a literature review in which they identified 11 network meta-analyses evaluating the efficacy and safety of the novel oral anticoagulants for stroke prevention.[13] Per their appraisal, the meta-analyses are similar in their evidence base, but they differ in potential treatment effect modifiers regarding the mean time spent in therapeutic range (TTR) in the warfarin arms, risk of stroke of systemic embolism across trials, focus on primary vs. secondary stroke prevention, and type of populations analyzed. Differences among the individual clinical trials in TTR (44% to 68%)[23] as

well as baseline risk for stroke and estimates of efficacy were also cited as limitations.[13] Comparing the novel oral anticoagulants, Cope et al asserted that the efficacy of dabigatran 110 mg twice daily was similar to that of rivaroxaban and apixaban in terms of stroke of systemic embolism, while dabigatran 150 mg twice daily was associated with more favorable (though non-significantly) results. Similar effects were observed for all-cause mortality and cardiovascular death, with some analyses favoring dabigatran. With regard to myocardial infarction, the efficacy of dabigatran at both doses was unfavorable compared to rivaroxaban and apixaban. Notably, none of the meta-analyses evaluated by Cope et al included results from ENGAGE AF-TIMI (i.e., edoxaban data).

Based on Cope et al's findings, the novel oral anticoagulants appear to be similar in overall efficacy to warfarin in patients with atrial fibrillation.[13] However, the presence of significant heterogeneity among the individual trials preclude clear conclusions regarding comparative efficacy among the anticoagulants.

Safety concerns

The new oral anticoagulant agents are attractive alternatives to warfarin: they are associated with fewer drug-drug interactions, do not require laboratory monitoring (see Table 5), and may be easier to dose.[2-6] However, clinical experience with these drugs is comparatively lacking. All of the anticoagulants have been associated with bleeding events, ranging in severity from mild to fatal. Product-specific safety concerns are outlined in Table 6.[2-6]

Comparative safety in patients with atrial fibrillation

Safety outcomes were assessed in all of the 5 aforementioned phase 3 trials comparing novel oral anticoagulants to warfarin in patients with atrial fibrillation.[14-18] All trials reported major bleeding as an outcome (see Table 7). Major bleeding was defined similarly across studies as bleeding resulting in reduction in hemoglobin level of ≥ 2 g/dL, requiring transfusion of ≥ 2 units of blood, symptomatic bleeding in a critical area or organ, or bleeding resulting in death (in line with criteria from the International Society on Thrombosis and Haemostasis). Compared to warfarin, the higher doses of rivaroxaban (20 mg/day) and dabigatran (150 mg twice daily) resulted in increased, though non-statistically significant, rates of major bleeding.[14,15] The results were similar for comparisons of major and non-major bleeding rates.

Loffredo et al sought to determine whether the novel oral anticoagulants are associated with an increased risk of gastrointestinal bleeding compared to warfarin.[24] They conducted a meta-analysis of 4 phase 3 trials (RE-LY, ROCKET-AF, ARISTOTLE, and ENGAGE-AF-TIMI) and determined that overall, there was an increased risk with the novel agents (relative risk [RR] 1.23; 95% confidence interval [CI] 1.03 to 1.46). Among the 4 agents, rivaroxaban (RR 1.46; 95% CI 1.2 to 1.8), and high doses of edoxaban (60 mg daily; RR 1.22, 95% CI 1.01 to 1.47) and dabigatran (150 mg twice daily; RR 1.50; 95% CI 1.20 to 1.88) were associated with an elevated risk of gastrointestinal bleeding compared to warfarin. A null effect was observed with apixaban compared to warfarin (RR 0.879; 95% CI 0.677 to 1.140). The investigators noted, however, that there was substantial heterogeneity among the studies ($I^2=80$, p=0.001).

More recently, Renda et al conducted a meta-analysis evaluating the net clinical benefit of the novel oral anticoagulants compared to warfarin in the same 4 phase 3 trials.[25] They considered the following outcomes: ischemic stroke, systemic embolism, myocardial infarction, hemorrhagic stroke, and adjusted major bleeding. They calculated the crude incidence rate (IR) per 100-patient years for each event and determined the net clinical benefit to be the weighted sum of IRs in the warfarin groups minus the weighted sum of IRs in the non-VKA oral anticoagulant groups (see Table 8). Weights were used to balance events in terms of "ischemic stroke equivalents" and were determined based on an analysis of the RE-LY trial.[26] Based on their calculations, Renda et al determined that all of the non-VKA agents were associated with a lower rate of ischemic stroke equivalents compared to warfarin, suggesting an improved efficacy/safety balance with the novel agents.[25] Among them, apixaban and low-dose edoxaban were associated with the lowest risk of adverse events. However, they acknowledged that not all events were reported similarly across the trials, and that the outcomes were determined using weights that were based on 1 study analysis. The authors hypothesized that the weights would have been more accurate had they been based on the rates of death associated with the events reported in each trial.

Reversal agents

Not all of the anticoagulants have specific or established antidotes (see Table 9). Per Ansell, most authorities recommend use of prothrombin complex concentrates (e.g., Kcentra®; containing factors II, VII, IX, X, and proteins C and S) to manage life-threatening bleeding with the novel oral anticoagulants, but the evidence to support their use in this regard is lacking.[27,28] At this time, only dabigatran has a specific reversal agent: idarucizumab (Praxbind®).[29] Two other antidotes are in development and currently in phase 3 trials: andexanet, a truncated form of factor Xa, and ciraparantag, a synthetic small molecule targeted to reverse direct thrombin inhibitors, factor Xa inhibitors, and indirect inhibitor enoxaparin.[30]

Summary

In summary, there are several novel oral anticoagulants to consider, alternative to VKA and parenteral agents. While all carry a risk of bleeding, there may be advantages compared to older agents with regard to ease of dosing, monitoring, and potential drug interactions. However, not all agents have specific or established antidotes, and clinical experience with these drugs is also limited. Further studies are necessary to better characterize their benefits and risks and place in therapy.

Table 1. FDA-approved uses and dosing of oral anticoagulants.[2-6]

Drug name (brand, manufacturer)	Mechanism of action	Product availability	FDA indications	Adult dosage	Special dosing considerations
Apixaban (Eliquis®, Bristol-Myers Squibb)	Factor Xa inhibitor	2.5 and 5 mg tablets	• Reduction of the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation • Prophylaxis of DVT, which may lead to PE, in patients who have undergone hip or knee replacement surgery • Treatment of DVT and PE • Reduction in risk of recurrent DVT and PE following initial therapy	• Nonvalvular atrial fibrillation: 5 mg twice daily • Prophylaxis of DVT following hip/knee replacement: 2.5 mg twice daily • Treatment of DVT and PE: 10 mg twice daily for first 7 days, then 5 mg twice daily • Reduction in risk of recurrent DVT and PE: 2.5 mg twice daily	• 2.5 mg twice daily recommended in patients with 2 or more of following: age ≥80 years, body weight ≤60 kg, Scr ≥1.5 mg/dL • Avoid use in patients with severe hepatic impairment • May be taken with or without food
Dabigatran (Pradaxa®, Boehringer Ingelheim)	Direct thrombin inhibitor	75, 110, and 150 mg capsules	• Reduction of the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation • Prophylaxis of DVT and PE in patients who have undergone hip replacement surgery • Treatment of DVT and PE in patients previously treated with a parenteral anticoagulant for 5-10 days • Reduction in risk of recurrent DVT and PE following initial therapy	• Nonvalvular atrial fibrillation: 150 mg twice daily • Prophylaxis of DVT and PE following hip replacement: 110 mg on first day, then 220 mg once daily • Treatment of DVT and PE: 150 mg twice daily after 5-10 days of parenteral anticoagulation • Reduction in risk of recurrent DVT and PE: 150 mg twice daily	• Nonvalvular atrial fibrillation: 75 mg twice daily recommended in patients with Clcr 15-30 mL/min • All other indications: dosing recommendations for patients with Clcr ≤30 mL/min or on dialysis are not provided • May be taken with or without food

Drug name (brand, manufacturer)	Mechanism of action	Product availability	FDA indications	Adult dosage	Special dosing considerations
Edoxaban (Savaysa®, Daiichi Sankyo)	Factor Xa inhibitor	15, 30, and 60 mg tablets	• Reduction of the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation • Treatment of DVT and PE in patients previously treated with a parenteral anticoagulant for 5-10 days	• Nonvalvular atrial fibrillation: 60 mg once daily • Treatment of DVT and PE: 60 mg once daily	• Nonvalvular atrial fibrillation: do not use drug if Clcr >95 mL/min; reduce dose to 30 mg once daily for patients with Clcr 15-50 mL/min • Treatment of DVT and PE: 30 mg once daily for patients with Clcr 15-50 mL/min or body weight ≤60 kg, or if using certain P-gp inhibitors • Avoid use in patients with moderate or severe hepatic impairment • May be taken with or without food
Rivaroxaban (Xarelto®, Janssen)	Factor Xa inhibitor	10, 15, and 20 mg tablets	• Reduction of the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation • Prophylaxis of DVT, which may lead to PE, in patients undergoing hip or knee replacement surgery • Treatment of DVT and PE • Reduction in risk of recurrent DVT and PE	• Nonvalvular atrial fibrillation: 20 mg once daily in the evening • Prophylaxis of DVT following hip/knee replacement: 10 mg once daily • Treatment of DVT and PE: 15 mg twice daily for first 21 days, then 20 mg daily • Reduction in risk of recurrent DVT and PE: 20 mg daily	• Nonvalvular atrial fibrillation: 15 mg daily in patients with Clcr 15-50 mL/min • Other indications: Avoid use in patients with Clcr <30 mL/min • Avoid use in patients with moderate or severe hepatic impairment • Take 15 and 20 mg tablets with food, 10 mg with or without food

Drug name (brand, manufacturer)	Mechanism of action	Product availability	FDA indications	Adult dosage	Special dosing considerations
Warfarin (Coumadin®, Bristol-Myers Squibb)	Vitamin K antagonist	1, 2, 2.5, 3, 4, 5, 6, 7.5, and 10 mg tablets	• Treatment and prevention of VTE • Treatment and prevention of thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement • Reduction in risk of death, recurrent MI, and thromboembolic events after MI	Individualize and adjust based on INR	• No dose adjustment necessary in renal impairment • Use caution in patients with hepatic impairment • Avoid in pregnancy • Caution ingestion of vitamin K-containing foods and interacting medications

Clcr=creatinine clearance; DVT=deep vein thrombosis; FDA=Food and Drug Administration; INR=international normalized ratio; MI=myocardial infarction; P-gp=p-glycoprotein; PE=pulmonary embolism; Scr=serum creatinine; VTE=venous thromboembolism

Table 2. ACCP 2012 recommendations on antithrombotic therapy for selected conditions, with 2016 update on treatment of VTE.[1,7-11]

Condition	ACCP recommendations
VTE prevention – orthopedic surgery	• THA/TKA: Use 1 of the following: LMWH, fondaparinux, dabigatran, apixaban, rivaroxaban, low-dose UFH, VKA, aspirin, or IPCD. **LMWH preferred to all**, irrespective of IPCD. Minimum duration 10 to 14 days. • Hip fracture surgery: Use 1 of the following: LMWH, fondaparinux, low-dose UFH, VKA, aspirin, or IPCD. **LMWH preferred to all**, irrespective of IPCD. • Consider extending duration of therapy to 35 days post-operatively for major surgery. • For patients at increased risk of bleeding, consider IPCD or no prophylaxis. • For patients with contraindications to suggested drugs or mechanical therapy, place IVC filter.
VTE prevention – non-orthopedic surgery (general, abdominal-pelvic)	• Mechanical prophylaxis with IPCD preferred for low-risk VTE (1.5%). • LMWH, low-dose UFH, or IPCD recommended for moderate-risk VTE (~3%). • LMWH or low-dose UFH in conjunction with IPCD recommended for high-risk VTE (~6%). • For patients at high risk of bleeding, consider IPCD. • Consider extending duration of therapy to 4 weeks with LMWH in patients at high risk for VTE with cancer. • **No mention of novel oral anticoagulants.**
VTE prevention – medical (non-surgical)	• Pharmacologic prophylaxis only recommended for acutely ill patients at increased risk of VTE who are not bleeding/without high risk for bleeding. • Recommended drugs: LMWH, low-dose UFH (BID or TID), or fondaparinux. • **No mention of novel oral anticoagulants.**

Condition	ACCP recommendations

VTE treatment*	• **DVT of the leg or PE, no cancer: dabigatran, rivaroxaban, apixaban, or edoxaban recommended over VKA for long-term (3 months) therapy. VKA therapy recommended over LMWH**. Note: initial parenteral anticoagulant therapy is administered before dabigatran and edoxaban, but is not given before rivaroxaban and apixaban, and is overlapped with VKA therapy.
	• **DVT of the leg or PE, with cancer: LMWH recommended over VKA therapy, dabigatran, rivaroxaban, apixaban, or edoxaban.**
	• DVT of the leg (proximal) or PE, unprovoked: in patients who stop anticoagulant therapy, aspirin recommended over no aspirin, if not contraindicated, to prevent recurrent VTE.
	• Duration of therapy:
	  o 3 months for patients with proximal DVT of the leg or PE provoked by surgery or nonsurgical transient risk factor.
	  o 3 months for patients with isolated distal DVT of the leg provoked by surgery or nonsurgical transient risk factor.
	  o 3 months for patients with second unprovoked VTE and high bleeding risk.
	  o At least 3 months for patients with unprovoked DVT of the leg (proximal or distal) or PE – patients should be re-evaluated for risk-benefit ratio of extended therapy at 3 months.
	  o At least 3 months for patients with second unprovoked VTE and moderate bleeding risk.
	  o Extended therapy (no scheduled stop date) for patients with first DVT of the leg or PE that is unprovoked and with low or moderate bleeding risk.
	  o Extended therapy for patients with second unprovoked VTE and with low bleeding risk.
	  o Extended therapy for patients with DVT of the leg or PE and active cancer, with or without high bleeding risk.

Stroke prevention	• **Dabigatran preferred to VKA in patients with history of ischemic stroke and atrial fibrillation.** • If intolerant of dabigatran or VKA, combination aspirin with clopidogrel recommended. • **No mention of other novel oral anticoagulants.**

BID=twice daily; DVT=deep vein thrombosis; IPCD=intermittent pneumatic compression device; IV=intravenous; IVC=inferior vena cava; LMWH=low molecular weight heparin; PE=pulmonary embolism; SC=subcutaneous; THA=total hip arthroplasty; TID=3 times daily; TKA=total knee arthroplasty; UFH=unfractionated heparin; VKA=vitamin K antagonist; VTE=venous thromboembolism

*Represents updated recommendations, published in 2016.

Table 3. Factors to consider when choosing initial and long-term therapy for VTE. Adapted from the ACCP 2016 guideline on VTE treatment.[11]

Factor	Preferred anticoagulant	ACCP comments
Cancer	LMWH	More so if: just diagnosed, extensive VTE, metastatic cancer, very symptomatic, vomiting, or on cancer chemotherapy.
Parenteral therapy to be avoided	Rivaroxaban, apixaban	VKA, dabigatran, and edoxaban require initial parenteral therapy.
Once daily oral therapy preferred	Rivaroxaban, edoxaban, VKA	--
Liver disease and coagulopathy	LMWH	NOACs contraindicated if INR raised because of liver disease; VKA difficult to control and INR may not reflect antithrombotic effect.
Renal disease and Clcr <30 mL/min	VKA	NOACs and LMWH contraindicated with severe renal impairment. Dosing of NOACs with levels of renal impairment differ with the NOAC and among institutions.
CAD	VKA, rivaroxaban, apixaban, edoxaban	Coronary artery events appear to occur more often with dabigatran than with VKA. This has not been seen with the other NOACs, and they have demonstrated efficacy for CAD. Antiplatelet therapy should be avoided if possible in patients on anticoagulants because of increased bleeding.
Dyspepsia or history of GI bleeding	VKA, apixaban	Dabigatran increased dyspepsia. Dabigatran, rivaroxaban, and edoxaban may be associated with more GI bleeding than VKA.
Poor adherence	VKA	INR monitoring can help to detect problems. However, some patients may be more adherent with an NOAC because it is less complex.
Thrombolytic therapy use	UFH infusion	Greater experience with its use in patients treated with thrombolytics.
Reversal agent needed	VKA, UFH	--
Pregnancy or pregnancy risk	LMWH	Potential for other agents to cross the placenta.
Cost, coverage, licensing	Varies among regions and with individual circumstances	--

ACCP=American College of Chest Physicians; CAD=coronary artery disease; Clcr=creatinine clearance; GI=gastrointestinal; INR=international normalized ratio; LMWH=low molecular weight heparin; NOACs=novel oral anticoagulants (i.e., apixaban, dabigatran, edoxaban, rivaroxaban); UFH=unfractionated heparin; VKA=vitamin K antagonist; VTE=venous thromboembolism

Table 4. Published phase 3 trials comparing novel oral anticoagulants to warfarin in patients with atrial fibrillation.[14-22]

Study	Design, duration	Population	Intervention	Endpoints	Selected baseline characteristics	Outcomes
RE-LY	MC, RCT, non-inferiority Median: 2 years	n=18,113 patients aged ≥18 yr with atrial fibrillation and ≥1 of following: • previous stroke or TIA • LVEF <40% • NYHA class II or higher within past 6 months • age ≥75 yr or 65-74 yr with DM, HTN, or CAD	Dabigatran 110 mg BID (n=6,015) Dabigatran 150 mg BID (n=6,076) Warfarin, dose adjusted to INR 2-3 (n=6,022) Concurrent ASA or other antiplatelet agents permitted	1°: stroke or systemic embolism 2°: stroke, death, MI, PE, hospitalization	• Mean age: 71 yr • Gender: 63.6% male • Mean $CHADS_2$ score: 2.1	1°: (dabigatran vs. warfarin, event rates in %/yr) • 110 mg: 1.53% vs. 1.69%; RR 0.91, 95% CI 0.74 to 1.11 • 150 mg: 1.11% vs. 1.69%; RR 0.66, 95% CI 0.53 to 0.82 2°: (dabigatran 150 vs. warfarin, RR and 95% CI) • Stroke: 0.64 (0.51 to 0.81) • MI: 1.38 (1.00 to 1.91) • PE: 1.61 (0.76 to 3.42) • Hospitalization: 0.97 (0.92 to 1.03) • Death (all-cause): 0.88 (0.77 to 1.00)
ROCKET AF	MC, DB, DD, RCT, non-inferiority Median: 590 days	n=14,264 patients aged ≥18 yr with nonvalvular atrial fibrillation and $CHADS_2$ score ≥2; i.e.: • history of stroke, TIA, or systemic embolism, or ≥2 of following: • HF or LVEF ≤35% • HTN • age ≥75 yr • DM	Rivaroxaban 20 mg daily, or 15 mg daily if Clcr 30-49 mL/min (n=7,131) Warfarin, dose adjusted to INR 2-3 (n=7,133)	1°: composite of stroke and systemic embolism 2°: stroke, systemic embolism, death, MI	• Median age: 73 yr • Gender: 60.3% male • Mean $CHADS_2$ score: 3.47	1°: (rivaroxaban vs. warfarin, number of events) • ITT: 269 vs. 306; HR 0.88, 95% CI 0.75 to 1.03 • PP: 188 vs. 241; HR 0.79, 95% CI 0.66 to 0.96 2°: (rivaroxaban vs. warfarin, HR and 95% CI) • Stroke: 0.85 (0.70 to 1.03) • Systemic embolism: 0.23 (0.09 to 0.61) • MI: 0.81 (0.63 to 1.06) • Death (all-cause): 0.85 (0.70 to 1.02)

Study	Design, duration	Population	Intervention	Endpoints	Selected baseline characteristics	Outcomes
J-ROCKET AF	MC, DB, DD, RCT, non-inferiority 30 months	n=1,278 patients aged ≥20 yr with nonvalvular atrial fibrillation and: • history of stroke, TIA, or non-CNS systemic embolism, or ≥2 of following: • HF or LVEF ≤35% • HTN • age ≥75 yr • DM	Rivaroxaban 15 mg daily, or 10 mg daily if Clcr 30-49 mL/min (n=639) Warfarin, dose adjusted to INR 2-3 if age <70 yr or INR 1.6-2.6 if age ≥70 yr (n=639)	1°: composite of stroke and systemic embolism 2°: stroke, systemic embolism, death, MI	• Mean age: 71 yr • Gender: 80.6% male • Mean $CHADS_2$ score: 3.25	1°: (rivaroxaban vs. warfarin, event rates in %/yr) • 1.26% vs. 2.61%, HR 0.49, 95% CI 0.24 to 1.00 2°: (rivaroxaban vs. warfarin, HR and 95% CI) • Stroke: 0.46 (0.22 to 0.98) • Systemic embolism: 1 vs. 1, HR not reported • MI: 3 vs. 1, HR not reported • Death (all-cause): 7 vs. 5, HR not reported
ARISTOTLE	MC, DB, DD, RCT, non-inferiority Median: 1.8 years	n=18,201 patients with atrial fibrillation or flutter and ≥1 of following: • age ≥75 yr • previous stroke, TIA, or systemic embolism • symptomatic HF within past 3 months or LVEF <40% • DM • HTN	Apixaban 5 mg BID or 2.5 mg BID if age ≥80 yr, body weight ≤60 kg, or Scr ≥1.5 mg/dL (n=9,120) Warfarin, dose adjusted to INR 2-3 (n=9,081)	1°: stroke or systemic embolism 2°: stroke, death, MI, PE or DVT	• Median age: 70 yr • Gender: 64.7% male • Mean $CHADS_2$ score: 2.1	1°: (apixaban vs. warfarin, event rates in %/yr) • 1.27% vs. 1.60%; HR 0.79, 95% CI 0.66 to 0.95 2°: (apixaban vs. warfarin, HR and 95% CI) • Stroke: 0.79 (0.65 to 0.95) • MI: 0.88 (0.66 to 1.17) • PE or DVT: 0.78 (0.29 to 2.10) • Death (all-cause): 0.89 (0.80 to 0.998)

Study	Design, duration	Population	Intervention	Endpoints	Selected baseline characteristics	Outcomes
ENGAGE AF-TIMI	MC, DB, DD, RCT, non-inferiority Median: 907 days	n=21,105 patients aged ≥21 yr with atrial fibrillation and CHADS$_2$ score ≥2; i.e.: • history of stroke, TIA, or systemic embolism, or ≥2 of following: • HF • HTN • age ≥75 yr • DM	Edoxaban* 30 mg daily (n=7,034) Edoxaban* 60 mg daily (n=7,035) *Dose halved if Clcr 30-50 mL/min, body weight ≤60 kg, or concurrent use of verapamil, quinidine, or dronedarone Warfarin, dose adjusted to INR 2-3 (n=7,036)	1°: time to first stroke or systemic embolism 2°: composite of stroke, systemic embolism, and CV death, major cardiac event	• Median age: 72 yr • Gender: 55.8% male • Mean CHADS$_2$ score: 2.8	1°: (edoxaban vs. warfarin, event rates in %/yr) • 30 mg: 1.61% vs. 1.50%; HR 1.07, 95% CI 0.87 to 1.31 • 60 mg: 1.18% vs. 1.50%; HR 0.79, 95% CI 0.63 to 0.99 2°: (edoxaban 60 mg vs. warfarin, HR and 95% CI) • Stroke: 0.88 (0.75 to 1.03) • Systemic embolism: 0.65 (0.34 to 1.24) • Cardiac event: 0.88 (0.81 to 0.97) • Composite: 0.87 (0.78 to 0.96)

CAD=coronary artery disease; CHADS$_2$=congestive heart failure, hypertension, age=75 years, diabetes mellitus, stroke – scoring system for estimating stroke risk; CI=confidence interval; Clcr=creatinine clearance; CV=cardiovascular; DB=double-blind; DD=double-dummy; DM=diabetes mellitus; DVT=deep vein thrombosis; HF=heart failure; HR=hazard ratio; HTN=hypertension; INR=international normalized ratio; ITT=intention-to-treat; LVEF=left ventricular ejection fraction; MC=multicenter; MI=myocardial infarction; NYHA=New York Heart Association; PE=pulmonary embolism; PP=per-protocol; RCT=randomized controlled trial; RR=relative risk; Scr=serum creatinine; TIA=transient ischemic attack

Table 5. Laboratory monitoring of oral anticoagulants.[2-6]

Drug name (brand, manufacturer)	Manufacturer recommendations
Apixaban (Eliquis®, Bristol-Myers Squibb)	• No laboratory parameters specified. • Apixaban may prolong PT, INR, and aPTT. Changes observed at the expected therapeutic dose are small, subject to much variability; thus, these tests are not useful in monitoring the anticoagulation effect of apixaban.
Dabigatran (Pradaxa®, Boehringer Ingelheim)	• aPTT and ECT may provide an approximation of dabigatran's anticoagulant effect. • Advice cannot be provided on goal levels of aPTT, but the average time course curve for effects on aPTT (available in product labeling) can be used to estimate the time to attain a particular level of aPTT. • ECT is more specific measure of dabigatran than aPTT. • At recommended doses, dabigatran prolongs aPTT, ECT, and TT.
Edoxaban (Savaysa®, Daiichi Sankyo)	• No laboratory parameters specified. • The anticoagulant effect cannot be reliably monitored with standard laboratory testing.
Rivaroxaban (Xarelto®, Janssen)	• No laboratory parameters specified. • The anticoagulant effect cannot be reliably monitored with standard laboratory testing.
Warfarin (Coumadin®, Bristol-Myers Squibb)	• INR – obtain daily INR upon initiation until stable in therapeutic range. Obtain subsequent measurements every 1 to 4 weeks. Perform additional measurements when warfarin products are interchanged, and when other medications are initiated, discontinued, or taken irregularly.

aPTT=activated partial thromboplastin time; ECT=ecarin clotting time; INR=international normalized ratio; PT=prothrombin time; TT=thrombin time

Table 6. Selected safety concerns of oral anticoagulants.[2-6]

Drug name (brand, manufacturer)	Boxed warnings	Contraindications	Adverse reactions	Drug interactions
Apixaban (Eliquis®, Bristol-Myers Squibb)	• Premature discontinuation of the drug increases the risk of thrombotic events. • Epidural or spinal hematomas may occur in patients receiving neuraxial anesthesia or undergoing spinal puncture.	• Active pathological bleeding • Severe hypersensitivity to apixaban	• Most common and most serious: bleeding-related (>1%) • Hypersensitivity reactions (<1%)	• Concomitant use of drugs affecting hemostasis (e.g., ASA, other anticoagulants, NSAIDs) – increased risk of bleeding. • Strong CYP3A4 and P-gp inhibitors (e.g., ketoconazole, ritonavir, clarithromycin) – increased exposure to apixaban. Decrease dose to 2.5 mg twice daily. • Strong CYP3A4 and P-gp inducers (e.g., rifampin, carbamazepine) – decreased exposure to apixaban. Avoid concomitant use.
Dabigatran (Pradaxa®, Boehringer Ingelheim)		• Active pathological bleeding • Severe hypersensitivity to dabigatran • Mechanical prosthetic heart valve	• Most common: gastritis-like symptoms (e.g., dyspepsia, GERD, esophagitis, GI ulcer) and bleeding (>15%) ▪ Risk of bleeding increases with age • Hypersensitivity reactions (<0.1%) • Post-marketing: angioedema, thrombocytopenia, esophageal ulcer	• P-gp inducers (e.g., rifampin, carbamazepine) – decreased exposure to dabigatran. Avoid concomitant use. • P-gp inhibitors dronedarone and systemic ketoconazole (do not extrapolate to other P-gp inhibitors) o In patients with Clcr 30 to 50 mL/min, reduce dose of dabigatran to 75 mg twice daily. o In patients with Clcr <30 mL/min, do not use dabigatran.

Drug name (brand, manufacturer)	Boxed warnings	Contraindications	Adverse reactions	Drug interactions

Edoxaban (Savaysa®, Daiichi Sankyo)	• Reduced efficacy of edoxaban in patients with nonvalvular atrial fibrillation and Clcr >95 mL/min.
	• Premature discontinuation of the drug increases the risk of ischemic events.
	• Epidural or spinal hematomas may occur in patients receiving neuraxial anesthesia or undergoing spinal puncture.
		• Active pathological bleeding	• Most common:
			  ○ In patients with nonvalvular atrial fibrillation: bleeding and anemia (≥5%)
			  ○ In patients with DVT/PE: bleeding, rash, abnormal liver function tests, anemia (≥1%)
				• Anticoagulants – avoid concomitant use.
				• Rifampin – avoid concomitant use.

Rivaroxaban (Xarelto®, Janssen)	• Premature discontinuation of the drug increases the risk of thrombotic events. • Spinal/epidural hematomas have occurred in patients receiving neuraxial anesthesia or undergoing spinal puncture.	• Active pathological bleeding • Severe hypersensitivity to rivaroxaban • Prosthetic heart valve (relative contraindication)	• Most common: bleeding (>5%) • Increased risk of stroke after discontinuation in patients with nonvalvular atrial fibrillation (observed in clinical trials when transitioned from rivaroxaban to warfarin) • Post-marketing: agranulocytosis, thrombocytopenia, retroperitoneal hemorrhage, jaundice, cholestasis, hepatitis, hypersensitivity, angioedema, cerebral hemorrhage, subdural hematoma, hemiparesis, Stevens-Johnson syndrome	• Combined P-gp and strong CYP3A4 inhibitors or inducers – avoid concomitant use. • Anticoagulants – avoid concomitant use.

Drug name (brand, manufacturer)	Boxed warnings	Contraindications	Adverse reactions	Drug interactions
Warfarin (Coumadin®, Bristol-Myers Squibb)	• Major or fatal bleeding. • Perform regular monitoring of INR in all patients. • Drugs, dietary changes, and other factors affect INR levels. • Instruct patients about prevention measures to minimize risk of bleeding and to report signs/symptoms of bleeding.	• Pregnancy, except in women with mechanical heart valves • Blood dyscrasias • Recent or contemplated surgery of CNS, eye, or traumatic surgery • Bleeding tendencies • Threatened abortion, eclampsia, pre-eclampsia • Unsupervised patients with potential high levels of nonadherence • Spinal puncture • Procedures with potential for uncontrollable bleeding • Hypersensitivity to warfarin • Major regional/lumbar block anesthesia • Malignant hypertension	• Most common: fatal and nonfatal hemorrhage from any tissue/organ • Skin necrosis • Systemic atheroemboli • Hypersensitivity reactions • Vasculitis • Hepatitis (cholestatic) • GI disorders (nausea, vomiting, diarrhea, taste disturbance, abdominal pain) • Respiratory disorders (tracheal calcification)	• Inhibitors and inducers of CYP2C9, 1A2, or 3A4 – altered warfarin exposure. Monitor INR closely. • Drugs increasing bleeding risk (e.g., other anticoagulants, NSAIDs, antiplatelet drugs, serotonin reuptake inhibitors). • Antibiotics and antifungals – altered warfarin exposure. Monitor INR closely when starting/stopping antimicrobial. • Herbal products and vitamin K-containing foods – altered warfarin effects. Monitor INR closely when starting/stopping herbal products and with dietary changes.

ASA=aspirin; Clcr=creatinine clearance; CNS=central nervous system; CYP=cytochrome P450; DVT=deep vein thrombosis; GERD=gastroesophageal reflux disease; GI=gastrointestinal; INR=international normalized ratio; NSAIDs=non-steroidal anti-inflammatory drugs; P-gp=p-glycoprotein; PE=pulmonary embolism

Table 7. Selected safety outcomes from phase 3 trials comparing novel oral anticoagulants to warfarin in patients with atrial fibrillation.[14-18]

Study	Novel oral anticoagulant*	Event rate (%/yr)		Hazard ratio (95% CI)
		Novel agent	Warfarin	
Major bleeding**				
RE-LY	Dabigatran 110 mg BID	2.71%	3.36%	0.80 (0.69-0.93)
	Dabigatran 150 mg BID	3.11%	3.36%	1.16 (1.00-1.34)
ROCKET AF	Rivaroxaban 20 mg daily	5.6%	5.4%	1.04 (0.90-1.20)
J-ROCKET AF	Rivaroxaban 15 mg daily	3.59%	3.31%	Not reported
ARISTOTLE	Apixaban 5 mg BID	2.13%	3.09%	0.69 (0.60-0.80)
ENGAGE AF-TIMI	Edoxaban 30 mg daily	1.61%	3.43%	0.47 (0.41-0.55)
	Edoxaban 60 mg daily	2.75%	3.43%	0.80 (0.71-0.91)
Major or clinically relevant non-major bleeding				
RE-LY***	Dabigatran 110 mg BID	14.62%	18.15%	0.78 (0.74-0.83)
	Dabigatran 150 mg BID	16.42%	18.15%	1.16 (1.09-1.23)
ROCKET AF	Rivaroxaban 20 mg daily	20.7%	20.3%	1.03 (0.96-1.11)
J-ROCKET AF	Rivaroxaban 15 mg daily	Not reported		
ARISTOTLE	Apixaban 5 mg BID	4.07%	6.01%	0.68 (0.61-0.75)
ENGAGE AF-TIMI	Edoxaban 30 mg daily	7.97%	13.02%	0.62 (0.57-0.67)
	Edoxaban 60 mg daily	11.10%	13.02%	0.86 (0.80-0.92)

BID=twice daily; CI=confidence interval
*Compared to warfarin, dose-adjusted based on INR
**Defined according to criteria from the International Society on Thrombosis and Haemostasis
***Major or minor bleeding

Table 8. Crude incidence rates of selected safety outcomes reported by Renda et al.[25]

Study - drug	Ischemic stroke	Systemic embolism	MI	Hemorrhagic stroke	Adjusted major bleeding	Net clinical benefit (95% CI)
Weight*	1.00	0.61	0.89	3.23	0.63	N/A
RE-LY						
Dabigatran 110 mg	1.34	0.07	0.73	0.39	1.72	-0.82 (-1.37, -0.27)
Dabigatran 150 mg	0.92	0.07	0.72	0.32	2.02	-1.02 (-1.56, -0.48)
Warfarin	1.21	0.10	0.57	1.23	1.97	N/A
ROCKET-AF						
Rivaroxaban	1.40	0.02	0.81	0.84	2.10	-0.74 (-1.29, -0.17)
Warfarin	1.52	0.12	1.00	1.42	1.86	N/A
ARISTOTLE						
Apixaban	0.97	0.05	0.47	0.78	1.19	-1.36 (-1.80, -0.92)
Warfarin	1.05	0.06	0.54	1.52	1.65	N/A
ENGAGE AF-TIMI						
Edoxaban 30 mg	1.77	0.09	0.79	0.52	0.91	-1.29 (-1.72, -0.86)
Edoxaban 60 mg	1.25	0.05	0.62	0.84	1.57	-1.04 (-1.48, -0.61)
Warfarin	1.25	0.07	0.67	1.52	1.86	N/A

CI=confidence interval; MI=myocardial infarction; N/A=not applicable
*Assigned by meta-analysis investigators, as determined from an analysis of the RE-LY trial.[26]

Table 9. Antidotes for oral anticoagulants.[2-6]

Drug name (brand, manufacturer)	Manufacturer recommendations
Apixaban (Eliquis®, Bristol-Myers Squibb)	• A specific antidote is not available. • Use of prothrombin complex concentrate, activated prothrombin complex concentrate, or recombinant factor VIIa may be considered but has not been evaluated in clinical studies. • Protamine sulfate and vitamin K are NOT expected to reverse the anticoagulant effects of apixaban. There is no role for systemic hemostatics (e.g., desmopressin, aprotinin).
Dabigatran (Pradaxa®, Boehringer Ingelheim)	• Use idarucizumab (Praxbind®) in case of emergency surgery or urgent procedures when reversal of the anticoagulant effect is needed.
Edoxaban (Savaysa®, Daiichi Sankyo)	• A specific antidote is not available. • Protamine sulfate, vitamin K, and tranexamic acid are NOT expected to reverse the anticoagulant effects of edoxaban.
Rivaroxaban (Xarelto®, Janssen)	• A specific antidote is not available. • Partial reversal of PT prolongation has been observed with use of prothrombin complex concentrates in healthy volunteers. • Protamine sulfate and vitamin K are NOT expected to reverse the anticoagulant effects of apixaban.
Warfarin (Coumadin®, Bristol-Myers Squibb)	• Vitamin K (oral or parenteral)

PT=prothrombin time

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