

Anticoagulation Options for Patients with Non-Valvular Atrial Fibrillation

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Patients with atrial fibrillation are at an increased risk of stroke and systemic embolic events. Anticoagulation therapy significantly reduces such risks and is an integral part of standard of care for patients with atrial fibrillation. Increased anti-coagulation options for patients with atrial fibrillation, particularly with the introduction and increased usage of novel oral anticoagulants, has made it imperative for primary care physicians to understand the risks and benefits of newer options of anticoagulation. Primary and secondary outcome data from head-to-head trials between warfarin and newer anticoagulants have been reviewed and summarized in this article. Based on the data from four robust clinical trials; dabigatran, rivaroxaban, apixaban, and edoxaban are either non-inferior or even superior to warfarin in preventing stroke or systemic embolic events. All newer oral anticoagulants were associated with a significantly lower rate of intracranial hemorrhage compared to warfarin. Overall major bleeding was less with all newer anticoagulants but gastrointestinal bleeding was significantly less with warfarin compared to dabigatran and rivaroxaban. Better safety profile with newer anticoagulants comes with a higher cost. Choice of anticoagulant should be a shared-decision between patients and their health care providers. Lack of a specific antidote, shorter half-life compared to warfarin and lack of long-term safety data are some of the issues with newer anti-coagulants that patients should be informed about.

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shorter half-life compared to warfarin and lack of long-term safety data are some of the issues with newer anti-coagulants that patients should be informed about.

INTRODUCTION

Atrial fibrillation (AF) increases the risk of ischemic stroke by almost five times. A clot as small as 2 mm, formed in the heart of patients with AF, may potentially dislodge and cause a stroke or major systemic embolic event (SEE). In individuals between 50-59 years of age, AF accounts for about 1.5% of strokes. About 23.5% of strokes in individuals between the ages of 80-90 are related to AF.^{1,2} The thirty-day mortality rate of patients with AF from stroke is about 24%. Overall mortality from AF alone is increased by 40-90%.³ The lifetime risk of developing AF at age 40 is 23%-26%,⁴ and the projected number of Americans who will be diagnosed with AF by 2050 is about ten million.⁵

Well designed population based studies such as the Framingham study, cardiovascular health study, Mayo Clinic study, and Western Australian study have indicated that by age 80 approximately 10-15% of individuals will have AF, most of whom will require oral anti-coagulation therapy.⁶

The decision to initiate anticoagulation therapy in patients with AF should be based on CHADS2 (congestive heart failure, hypertension, age>75, diabetes, stroke) or CHA2DS2-VASc (vascular disease, age and sex) score.⁷ The ACC/AHA in

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partnership with the European Society of Cardiology and the European Heart Rhythm Society recommend anticoagulation in all types of AF with a CHADS2 score of ≥ 1 . For patients with a score of 0, aspirin 81-325 mg a day is a reasonable choice, though anticoagulation is an appropriate option. Life-long anticoagulation therapy in patients with AF significantly decreases thrombosis and SEE (American College of Cardiology/American Heart Association; ACC/AHA; Class I, Level A; European Society of Cardiology Class I, Level A).⁸

According to the Garfield registry, which includes data from nineteen different countries, more than 10% of patients with AF and a CHADS2 score of 2 or more were not on any anticoagulant.⁹ For primary care physicians and cardiologists, finding a balance between preventing major thromboembolic events from AF and a major bleeding event from oral anticoagulation is a challenging, yet imperative task.

Between 1989 and 1993, six clinical trials involving about 2,900 patients compared warfarin to placebo for stroke prevention in patients with AF. Between 2008 and 2013 new class or novel oral anti-coagulants (NOACs) like dabigatran, apixaban, rivaroxaban, edoxaban, betrixaban and darexaban were compared to the adjusted dose of warfarin for stroke or SEE prevention in patients with AF.

Based on the results from these trials, in 2010 the United States Food and Drug Administration (USFDA), approved the first NOAC, dabigatran etexilate, for patients with non-valvular AF for the prevention of stroke/SEE. Other NOACs approved by the USFDA for the same indication are direct factor Xa inhibitors rivaroxaban and apixaban. Edoxaban has shown promising results, however, its use in the U.S. has not yet been approved.

WARFARIN

Warfarin (Coumadin) is a vitamin K antagonist and inhibits the action of factors II, VII, IX and X, protein C and S. Since its discovery for medicinal use, warfarin has been the most commonly prescribed oral anticoagulant. Warfarin decreases the risk of stroke/SEE in patients with AF by 64% (95% CI, 49% to 74%) compared to placebo.^{10,11} When administered orally warfarin is almost completely absorbed and time to reach maximum plasma concentration (C_{max}) is about four hours, however its peak therapeutic effects reaches only 72-96 hours after oral administration. More than 90% of the drug is excreted in urine, mostly as inactive metabolites.

Due to warfarin's narrow therapeutic index, the recommended time in therapeutic range (TTR) for international normalized ratio (INR) is at least 70% during six straight months. The warfarin dose to keep INR within therapeutic range greatly varies between individuals, partly due to the different degree

of CYP2C9 and VKORC1 genes expressed. For reasons not clearly understood, elderly patients and Asians are more sensitive to the anticoagulant effects of warfarin.

Significant drug-drug interactions, drug-food interactions, narrow therapeutic index, life-long monitoring of INR, fluctuating INR values, slow onset and offset of action, and genetic variability have made warfarin a difficult drug to use safely. About 25,000 people in the U.S. are hospitalized annually from warfarin related adverse reactions, making it the number one drug-related emergency room visit requiring hospitalization.¹²

An alternative treatment to warfarin that is cost effective, possesses the ability to inhibit free and clot-bound thrombin with predictable pharmacokinetics and pharmacodynamics, has a specific antidote, does not require frequent monitoring and dosing adjustments, has a better safety profile, and is as efficacious as warfarin has been long overdue. Results from four trials (RE-LY for dabigatran, ROCKET-AF for rivaroxaban, ARISTOTLE for apixaban, and Engage AF-TIMI 48 for edoxaban) with NOACs are discussed below. These four clinical trials included 71,683 patients from several countries. The primary study outcome in all these trials was stroke or SEE. The primary safety outcome was major bleeding defined as ≥ 2 g/dL reduction in hemoglobin from baseline, transfusion of ≥ 2 units of blood, or symptomatic bleeding.

DABIGATRAN ETEXILATE

Dabigatran Etexilate Mesylate (Pradaxa) is a prodrug, which is converted to dabigatran, a direct competitive inhibitor of thrombin. Its bioavailability when administered orally is only about 3-7%, however if the capsule is broken or damaged before taking it, its bioavailability is increased to about 80%, which may increase the risk of clinically significant bleeding. Maximum serum concentration (C_{max}) after oral administration is about 1 hour. Co-administration of dabigatran with fatty food may prolong C_{max} to about 2 hours but does not change its bioavailability.

In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, a non-inferiority trial, 18,113 patients (mean age 71 yrs.) with non-valvular AF and mean CHADS2 score of 2.1 ± 1.1 were enrolled from 44 different countries. Dabigatran 110 mg or 150 mg twice daily administered in a blinded manner was compared to an adjusted warfarin dose given in an unblinded fashion to keep INR between 2.0-3.0 (mean TTR 64%). Mean duration of patient follow up was two years.¹³

Compared to dose adjusted warfarin, both doses of dabigatran lowered the primary efficacy rates of stroke/SEE in a dose dependent manner. Stroke/SEE rate was 1.11%

per year in the dabigatran 150 mg BID group; whereas the warfarin group experienced 1.69% per year rate (RR 0.66; 95% CI 0.53-0.82, $p < 0.001$ for inferiority). In the 110 mg BID group, stroke/SEE rate was 1.53% per year while the warfarin group saw a rate of 1.69% per year (RR 0.91; CI 95% 0.74-1.11, $p < 0.001$ for inferiority). The difference seen was statistically non-significant for dabigatran's superiority over warfarin. Authors of this study concluded that both doses of dabigatran were non-inferior to warfarin in regard to primary efficacy outcomes stroke/SEE in patients with AF ($p < 0.001$ for non-inferiority).¹³

Dabigatran exhibited statistically significant superiority to warfarin in reducing hemorrhagic (both doses) and ischemic (150 mg dose only) strokes. In the 150 mg group, hemorrhagic stroke rate compared to warfarin was 0.10 vs. 0.38% per year (RR 0.26; 95% CI 0.14-0.49, $p < 0.001$) and in the 110 mg group it was 0.12 vs. 0.38% per year (RR 0.31; 95% CI 0.17-0.56, $p < 0.001$).

A higher rate of gastrointestinal (GI) bleeding occurred in dabigatran groups in a dose dependent manner. Increase in GI bleeding rate was significantly higher with 150 mg of dabigatran (1.51 vs. 1.02% per year, RR 1.50; 95% CI 1.19-1.89, $p < 0.001$) but not with 110 mg (1.12 vs. 1.02% per year, RR 1.10; 95% CI 0.86-1.41, $p = 0.43$) when compared to warfarin. Higher GI bleeding with dabigatran is attributed to its tartaric acid core to enhance its absorption in the GI tract. Net clinical outcome (composite score of stroke, SEE, major bleeding and death) and overall major bleeding rates were similar in all three arms.¹³

For adult patients with AF and normal kidney function, dabigatran is prescribed in doses of 150 mg every 12 hours with or without food. Its half-life is about 12-17 hours and the kidney excretes 80% of the drug. Dose adjustment is recommended in patients with creatinine clearance (CrCl) less than 30 mL/min. For patients with CrCl between 30 and 50 mL/min who are on a P-glycoprotein inhibitor such as ketoconazole or dronedarone, 75 mg twice a day is the recommended dose. If CrCl is between 15-30 mL/min, dabigatran 75 mg twice a day is recommended but a P-glycoprotein inhibitor should be avoided. For patients with a CrCl less than 15 mL/min or those on dialysis, risk of using dabigatran may outweigh the benefit.¹⁴

If a scheduled dose is missed and the next dose is due in less than six hours then the missed dose should be skipped. It is recommended that Dabigatran be discontinued 1-2 days ($> \text{CrCl } 50 \text{ mL/min}$) or 3-5 days ($\text{CrCl } < 50 \text{ mL/min}$) preoperatively. When switching from warfarin to dabigatran, warfarin should be stopped and INR should be less than 2.0 before taking the first dose of dabigatran. When switching

from dabigatran to warfarin, starting time of warfarin depends on CrCl. If CrCl is $> 50 \text{ mL/min}$, warfarin should be started 3 days prior to stopping dabigatran. If CrCl is between 15-30 or 30-50 mL/min, warfarin should be started 1 or 2 days prior to stopping dabigatran, respectively. No recommendation has been given for those with CrCl less than 15 mL/min.¹⁴

Dabigatran prolongs ecarin clotting time (ECT), activated partial thromboplastin time (aPPT) and thrombin time (TT), and hypothetically these parameters could be used to assess degree of anticoagulation from dabigatran, but these tests are not standardized for this purpose and ECT is not a readily available in most of the clinics and hospitals. In case of overdose, dabigatran can be removed via hemodialysis but more data are needed to support this.¹⁵

RIVAROXABAN

Rivaroxaban (Xarelto) is a factor Xa inhibitor approved by the USFDA for use in patients with non-valvular AF, pulmonary embolism, and deep vein thrombosis prophylaxis and treatment. Its oral bioavailability is inversely proportional to its dose (66% for 20 mg tablet, 100% for 10 mg tablet). Rivaroxaban can be taken with or without food but food may increase the bioavailability of the 20 mg tablet by up to 39%. For those who cannot swallow the tablet, it may be crushed and mixed with food, however its storage half-life may decrease significantly once mixed with food. After oral administration time to reach C_{max} is 2-4 hours. About 66% of rivaroxaban is excreted into urine with 33% of the total in unchanged form.¹⁶ Rivaroxaban prolongs PT and aPTT. Anti-factor Xa assay is not recommended to be used to assess degree of anticoagulation.

A total of 14,264 patients with non-valvular AF were included in the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF). It was a randomized, double-blinded, double-dummy, multicenter, international trial. Rivaroxaban 20 mg once a day was compared to warfarin for its non-inferiority in preventing Stroke/SEE in patients with non-valvular AF. Mean CHADS2 score was 3.48 ± 0.94 which was comparable to the warfarin group. Mean TTR in the warfarin group was 55%. Mean duration of patient follow up was 2.3 years.¹⁷

Rivaroxaban was found to be non-inferior to warfarin for Stroke/SEE prevention. Stroke/SEE incidence percent per year was 2.2% in the warfarin group and 1.7% in the rivaroxaban treated patients (HR 0.79; 95% CI 0.66-0.96, $p < 0.001$ for non-inferiority). Rivaroxaban was associated with a significantly lower incidence of intracranial hemorrhage (0.7 vs. 0.5% per year, HR 0.67; 95% CI 0.47-0.93, $p < 0.02$). Similar to

dabigatran, rivaroxaban was associated with significantly higher rate of GI bleed (2.16 vs. 3.15% per year, $p < 0.001$). There was no significant difference in overall major bleeding rate between the two groups (3.4 vs. 3.6% per year, HR 1.04; 95% CI 0.90-1.20).¹⁷ All cause mortality was similar in both groups with event rate 1.87 vs. 2.21% per year (HR 0.85; 95% CI 0.70-1.02, $p < 0.073$).

Rivaroxaban is primarily metabolized by the liver and eliminated by the kidney (66%). Rivaroxaban dose and duration of administration depends on the indication for its use. As an anticoagulant for patients with non-valvular AF, the dose of rivaroxaban is based on CrCl value. If CrCl is above 50 mL/min, 20 mg a day is the recommended dose. 15 mg a day is an appropriate dose if CrCl is between 15-50 mL/min. Rivaroxaban is unsafe to use in patients with CrCl less than 15 mL/min.

If a dose of rivaroxaban is missed in patients with AF, it should be administered as soon as possible on the same day. When switching from warfarin to rivaroxaban, warfarin should be discontinued and rivaroxaban should be started as soon as INR is less than 3.0. If switching from rivaroxaban to warfarin, parenteral anticoagulation and warfarin should be started at the time the next dose of rivaroxaban would have been given. No data is available on whether bridging therapy can be done with rivaroxaban instead of parenteral anti-coagulation.

Use of rivaroxaban with P-gp and CYP3A4 inducers (carbamazepine, phenytoin, St. John's Wort) or inhibitors (ketoconazole, itraconazole, clarithromycin, conivaptan) should be avoided due to potential drug-drug interactions.

APIXABAN

Similar to dabigatran and rivaroxaban, apixaban (Eliquis) is absorbed rapidly after oral administration reaching its peak action within hours. Oral bioavailability is about 60%, renal elimination is about 27-35% of total clearance and its half-life is 12 hours. Food does not affect bioavailability and time to reach C_{max} after oral administration is 3-4 hours.¹⁸ Apixaban dosage should be decreased by 50% (2.5 mg twice daily) if patient is 80 years or older, has a body weight less than 60 kilogram, or serum Cr 1.5 mg/dL or higher.

Apixaban increases PT, aPTT and INR but none of them are recommended to use as a marker of degree of anti-coagulation. Unlike dabigatran and rivaroxaban, apixaban has not been shown, in vitro, to induce or inhibit P-glycoprotein, CYP2C9 and other CYP450 enzymes.

When switching from warfarin to apixaban, warfarin is discontinued and apixaban is started when INR is below 2.0. If switching from apixaban to warfarin, parenteral

anticoagulant and warfarin are started at the time the next dose of apixaban is due. Parenteral anticoagulant is discontinued once INR is in the therapeutic range. Apixaban is discontinued 24-48 hours before surgery and started again 24-48 hours after surgery.

In the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, apixaban 5 mg taken twice a day was compared with the adjusted dose of warfarin for the prevention of stroke/SEE in 5,599 patients with non-valvular AF and at least one additional risk factor for stroke. The INR was between 2.0-3.0 in patients on warfarin during 66% of the study period. The median duration of follow up in the ARISTOTLE trial was 1.8 years and the median age and mean CHADS₂ scores were 70 years and 2.1, respectively, in both groups.¹⁹

Apixaban decreased the risk of stroke/SEE by 21% when compared to warfarin. Event rate per year in the warfarin group was 1.60 vs. 1.27% per year in the apixaban group (HR 0.79; 95% CI 0.66-0.95, $p < 0.001$ for inferiority and $p < 0.01$ for superiority). Similarly, intracranial bleeding was significantly less (49% less) in the apixaban arm, 0.47 vs. 0.24% per year, (HR 0.51; 95% CI 0.35-0.75, $p < 0.001$ for superiority).¹⁹ Unlike with dabigatran and rivaroxaban, gastrointestinal bleeding was comparable in both groups. Net clinical outcome was significantly better with apixaban compared to warfarin (7.20 vs. 6.13; HR 0.85; 95% CI 0.78-0.92, $p < 0.001$).

EDOXYBAN

Edoxaban is a direct oral factor Xa reversible inhibitor. Oral bioavailability of edoxaban is 62% with rapid onset and offset of pharmacological action. Its half-life is 9-11 hours and the kidneys excrete 50%.

In The Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial, two doses of edoxaban (60 mg and 30 mg once daily), were compared to warfarin for the primary prevention of Stroke/SEE. This was a randomized, double-blinded, double dummy trial with 21,105 patients with a mean CHADS₂ score of 2.8 in all three groups. The mean time patients in the warfarin group had their INR between 2.0-3.0 was 64.9% of the treatment period. Median duration of follow up was 2.8 years.²⁰

Both doses of edoxaban were non-inferior to warfarin, but a higher dose was superior to warfarin in primary prevention. Annual event rate with edoxaban (60 mg once a day) was 1.18% per year compared to warfarin, which had a rate of 1.5% per year (HR 0.79; CI 95.5% 0.63-0.99; $p < 0.001$ for non-inferiority and $p < 0.02$ for superiority). Similar to the three other

NOACs discussed above, incidence of hemorrhagic stroke was significantly lower in both edoxaban groups compared to warfarin. Hemorrhagic stroke rate with 30 mg edoxaban was 0.16% per year while the 60 mg dose experienced a rate of 0.26% per year. There was a significantly lower rate of hemorrhagic stroke in both edoxaban groups compared to warfarin (by 65% less in 30 mg dose group and 44% less in 60 mg dose group). Hemorrhagic stroke rates in the edoxaban (30 mg dose) and the warfarin groups were 0.16% and 0.47% per year, respectively, (HR 0.33; 97.5% CI 0.22-0.50, $p < 0.001$) and it was 0.26% vs. 0.47% per year in 60 mg group (HR 0.54; 97.5% CI 0.38-0.77, $p < 0.001$).²⁰

Rate of GI bleeding with edoxaban was dose dependent. The edoxaban 60 mg dose was associated with a higher rate of GI bleed (1.23 vs. 1.51% per year, HR 1.23; 97.5% CI 1.02-1.50, $p = 0.03$) compared to warfarin. In the 30 mg edoxaban group, there was a significantly lower rate of GI bleed (1.23 vs. 0.83% per year, HR 0.67; 97.5% CI 0.53-0.83, $p < 0.001$) compared to the warfarin. Any major bleeding was significantly less with both doses of edoxaban when compared to warfarin. Net clinical outcomes were better with edoxaban compared to warfarin.²⁰

DISCUSSION

In a meta-analysis of 50,578 patients, results from RE-Ly (dabigatran), ROCKET-AF (rivaroxaban), and ARISTOTLE (apixaban) trials were compared to that of warfarin.²¹ There was an 18% reduction in primary efficacy outcome of stroke or SEE in the NOACs group (2.8% vs. 3.5% per year, OR 0.82, 95% CI 0.74-0.91, $p < 0.001$). The decrease in stroke seen in the NOAC group was driven by a decrease in hemorrhagic stroke. There was also a significant decrease in all cause mortality in the NOAC group (6.0 vs. 6.3% per year, OR 0.79, 95% CI 0.71-0.88, $p < 0.001$). No head to head clinical trial between different NOACs has been conducted to compare their primary or secondary outcomes.

Based on the data from four robust clinical trials with NOACs, dabigatran, rivaroxaban, apixaban, and edoxaban are either non-inferior or even superior to warfarin in preventing stroke or SEE in patients with AF with a CHADS2 score of at least 1. Only dabigatran taken at a dose of 150 mg twice a day dose was superior to warfarin in reducing ischemic stroke. All NOACs were associated with a significantly lower rate of intracranial hemorrhage compared to warfarin. Overall major bleeding was less with all NOACs but GI bleeding was significantly less with warfarin compared to dabigatran and rivaroxaban. Better safety profile with usage of NOACs may come with a higher monthly cost to health care providers and patients. Contrary to warfarin, NOACs do not have a specific approved antidote in the event of a major bleed. Due to rapid offset

of anticoagulation effect of NOACs (1-2 days) compared to warfarin (2-5 days), missing a single dose of this medication may potentially increase risk of stroke/SEE.

Rapid onset of pharmacological action, no need for INR monitoring, less frequent visits to an anti-coagulation clinic or physician's office, less interactions with other drugs and food make NOACs more attractive over warfarin. However, lack of a specific antidote for NOACs, standardized tests to assess the degree of anticoagulation from NOACs, shorter half-life compared to warfarin which may increase risk of blood clot when a dose is missed, lack of long term safety data, lack of data in patients with liver and renal dysfunction, during pregnancy, and in children are some of the concerning issues with NOACs. NOACs may be ideal for those with labile INR and low TTR. Overall treatment benefits of NOACs over warfarin are minute and depends on how well INR is within therapeutic range.²²

Whether NOACs or warfarin should be the first line treatment for patients with non-valvular AF is a shared-decision between patients and health care providers. Patients should be informed well about the costs, advantages and disadvantages of using NOACs or warfarin and patients' preference should be in the center of the decision-making process (Table 1). The American College of Chest Physicians recommends warfarin as the preferred initial treatment for patients with atrial fibrillation.²³ ACC/AHA recommends NOACs or a vitamin K antagonist (warfarin) as first line anti-coagulant therapy for patients with non-valvular AF with a CHADS2 score of 1 or higher.

All NOACs are transported in the GI tract by the P-gp transport efflux system, therefore drug-drug interaction (increased bleeding risk) is a real possibility when an NOAC is administered with a P-gp transport system inhibitor such as amiodarone, captopril, azithromycin, verapamil, diltiazem, and other medications. Rivaroxaban and apixaban but not dabigatran and edoxaban are substrates for CYP3A4 and therefore coadministration of an NOAC with a CYP3A4 inducer (carbamazepine, phenytoin, dexamethasone, and St. John's Wort) or inhibitor (clarithromycin, nefazodone, itraconazole, ketoconazole, and grape fruit juice) may significantly alter the pharmacokinetics of the NOAC and alter its therapeutic and adverse effects profile.²⁴

Those with mechanical valve or valvular AF are not candidates for NOACs and warfarin still may be a safer anticoagulant for such patients. There was a significantly increased rate of SEE and bleeding complications among patients with valvular AF who were on dabigatran compared to warfarin. This clinical trial was terminated prematurely.²⁵ To our knowledge, no such data has been published for other NOACs.

Table 1: Comparison of New Oral Anti-Coagulants and Warfarin

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Warfarin
Mechanism of action	Thrombin inhibitor	Factor Xa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor	Factor II, VII, IX, X, protein C & S
Prodrug	Yes	No	No	No	No
Bioavailability %	6	80	60	60	95%
Peak pharmacologic action (h)	1-2	2-4	3-4	1-2	72-96
Half-life (h)	12-17	7-11	12	9-11	40
Dosing	Fixed	Fixed	Fixed	Fixed	Variable
Dosing frequency	Once or Twice a day	Once or Twice a day	Twice a day	Once a day	Once a day
Renal clearance (%)	80	33	35	50	90
Monitoring	No	No	No	No	Yes
Antidote	No	No	No	No	Vitamin KK
Cost / month	\$280	\$280	\$145	Not available in U.S.	\$10**

** Cost to check INR is not included

SORT: Key Recommendations for Practice

Clinical Recommendation	Evidence rating	References
Novel oral anti-coagulant are recommended only for patients with non-valvular atrial fibrillation because mortality rate was higher with NOAC in patients with valvular atrial fibrillation.	A	13
In patients with non-valvular AF, anti-coagulation therapy significantly decreases stroke and systemic embolic events and is therefore recommended for most patients.	A	10,11
Novel oral anti-coagulants are non-inferior or superior to warfarin in preventing stroke or systemic emboli events in patients with non-valvular AF.	A	13,17,18
Clinically significant bleeding can occur with all oral anti-coagulation therapy. Warfarin has been shown to cause more hemorrhagic stroke compared to NOACs while gastrointestinal bleeding was less with warfarin.	A	13,17

A = consistent, good-quality patient-oriented evidence;

B = inconsistency or limited-quality patient-oriented evidence;

C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series.

For information about the SORT evidence rating system, go to <http://www.aafp.org/afpsort>.

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