Anticoagulation in Atrial Fibrillation

**Introduction**

AF decreases the pumping ability of the heart and may cause stagnation of the blood in the heart chambers. This increases the risk for stroke, myocardial infarction (MI) or "other embolic events from atrial thrombus." Overall, AF causes more than 20 percent of all stroke occurrences.1

AF may also increase heart rate and dysfunction of the left atrium and ventricle, contributing to the risk of developing heart failure.2

Some of the more common risk factors for AF include: hypertension, coronary heart disease with MI or congestive heart failure (CHF), valvular heart disease, sleep apnea, supraventricular tachycardia, hyperthyroidism, and excessive alcohol consumption.

Warfarin is the oldest of the anticoagulant medications used to inhibit clot formation reducing the risk of thrombotic events from AF. It is effective but requires continual and often frequent monitoring for safety use. For this reason, a number of new agents have been developed to simplify therapy. Warfarin remains, however, the only approved oral medication available to treat AF caused by valvular heart disease.

Newer anticoagulants that have been recently introduced to the market include: apixaban, rivaroxaban and dabigatran. Proper use of these agents will be reviewed in depth in this article.7

**CHADS2**

The American College of Chest Physicians (ACCP) uses a scoring system called the CHADS2 score to measure the risk for a future blood clot. This scoring system evaluates risk by assigning one point for each of the following risk factors: heart failure (HF), hypertension, age greater than or equal to 75 years, and diabetic. It assigns two points for patients with a prior history of stroke or transient ischemic attack (TIA).

The CHADS2 scoring system previously recommended anticoagulation therapy only if the score was greater than or equal to two, and aspirin or anticoagulation for a score of one. No anticoagulation was recommended for a score of zero.

The current 2012 ACCP guidelines revised this scoring system recommends anticoagulation for a score greater than equal to one; the aspirin recommendation for a score of one was discontinued.3

In the ATRIA study, the incidence of stroke for patients with a CHADS2 score of zero without the use of warfarin was 0.3 per 100 patients per year. With a score of 4 to 5, the incidence increased to 6.3 per 100 patients per year. This is a 21-fold increase in stroke risk; there are an additional 6 events per 100 patients per year with the higher CHADS2 score. This emphasizes the importance of anticoagulation in stroke prevention.5

**CHA2DS2-VASc**

In 2012, the European Society of Cardiology (ESC) began using a more rigorous scoring system, CHA2DS2-VASc. This scoring system assigns one point each for HF, hypertension and diabetes, and two points each for age greater than or equal to 75 years and history of stroke. It also assigns one point for vascular disease, age 65 to 74 and female gender.3

**CHADS2 vs. CHA2DS2-VASc**

The Atrial Fibrillation Network (AFNET) registry is the German Competence Network for AF. A five-year prospective follow-up study was conducted on 8,847 patients with non-valvular AF registered in the AFNET between 2004 and 2006. Patients with stroke, TIA or thromboembolic event during this time totaled 403; 36 percent of these patients had a CHADS2 score of 0 or 1. The CHA2DS2-VASc scoring was applied to these 145 patients; based on their CHA2DS2-VASc, oral anticoagulation would have been recommended for 126 of them. Further research may be needed to determine whether the CHA2DS2-VASc scoring system should supersede the CHADS2 system in future ACCP guidelines.

**WARFARIN**

The mechanism of action of warfarin (the generic name for Coumadin) is unique; it acts by inhibiting vitamin K epoxide reductase (VKORC1). VKORC1 is an important step in the activation of vitamin K dependent clotting factors II, VII, IX and X. Warfarin inhibits the production of VKORC1, thereby reducing the risk for a clot. Vitamin K dependent clotting factors are reduced by 30 percent to 50 percent with the use of warfarin. Some patients have variations in the VKORC1 gene which may require higher or lower doses of warfarin. Many food, drug and alternative medicine agents also can affect warfarin's effect.

Additionally, warfarin inhibits production of anticoagulant proteins C and S, which may increase the risk for clotting during the initiation of warfarin therapy. Depending on the circumstances, a parenteral anticoagulant may be used to bridge the patient during the first few days of warfarin therapy.8

Some of the U.S. Food and Drug Administration (FDA) approved indications for warfarin include: AF, deep vein thrombosis (DVT), pulmonary embolism, MI prophylaxis, stroke prophylaxis, and general thrombosis prophylaxis.6

Warfarin's duration of action is 2 to 5 days. If a patient misses a dose, it can and should be taken later that same day. If the day passes and no dose is taken, resume the regular dosing schedule on the next day. A double dose should NOT be taken the next day to compensate for the missed dose.8

The peak effect of warfarin occurs between 3 and 4 days following the first dose, although some immediate effects may occur in the first 24 hours. During warfarin initiation, lab measurement of the Prothrombin Time and International Ratio (PT/INR) should be monitored frequently. Monitoring frequency will decrease as the PT and INR stabilize. The PT/INR must be monitored on a regular basis for as long as the patient remains on warfarin.11

Patients should be instructed as to what side effects to monitor for and promptly report problems with bleeding events, including the subtle signs of stroke or gastrointestinal bleeding.

When the INR increases above goal; bleeding risk increases and a dose adjustment or withhold dose is recommended. When the INR increases dramatically, an antidote of vitamin K may be administered. If the elevated INR is accompanied by warfarin-associated major bleeding, vitamin K is recommended in addition to prothrombin complex concentrate (PCC). Vitamin K may take up to 24 hours to exhibit an
There are two isomers of warfarin, R and S with varying anticoagulation effects and CYP450 enzyme metabolizing rates. Therefore warfarin has many drug interactions with agents that compete with or induce the same enzyme systems. Some common interactions include: non-steroidal anti-inflammatory drugs (NSAIDs), anti-platelet agents, many antibiotics, corticosteroids, thiazide and loop diuretics, contraceptives, selective serotonin reuptake inhibitors, tramadol, amiodarone, dabigatran, and verapamil.

Many patients take herbal supplements; these need to be reviewed as many of them may interact with warfarin including: cranberry products, garlic, Ginkgo biloba, ginseng, herbal teas, Coenzyme Q10, St. John's wort, aloe, black cohosh, ginseng, licorice, and green tea.

Diet is an important aspect to consider when monitoring warfarin efficacy. Foods containing vitamin K may reduce the anticoagulant effect of warfarin. The warfarin dose may be adjusted to compensate so long as patients are consistent with their diet — foods containing vitamin K including spinach, kale, broccoli, brussel sprouts, mango, liver, nutritional supplements, etc. Always warn patients taking anticoagulant medications to check the labels on vitamin supplements to determine the vitamin K content.

Sudden smoking cessation (as may occur with an extended cold or asthma exacerbation) may increase the anticoagulation effect of warfarin and raise the risk of a bleed. Tobacco smoke may induce CYP450 enzymes which are partially responsible for warfarin metabolism. Additional INR monitoring may be warranted when a patient stops smoking. This applies even if a nicotine replacement product is used during the cessation process.

For patients with AF, believed to have been present for greater than 48 hours or duration unknown, anticoagulation must occur at least 3 weeks before a cardioversion procedure to avoid the risk of releasing a heart chamber thrombus. Another option is a transesophageal echocardiogram (TEE) with a short course of anticoagulation medication to rule out left atrial thrombi. If the cardioversion is successful in restoring a normal heart rhythm, anticoagulation may be discontinued after 4 weeks. For AF less than 48 hours, begin anticoagulation and proceed to cardioversion. Patients who continue to go in and out of an AF rhythm should remain on an anticoagulation agent.

After an ablation procedure to disrupt abnormal neural pathways causing AF, anticoagulation is still recommended by the CHADS2 score even if regular sinus rhythm is achieved. Other surgical and dental procedures may require temporary warfarin discontinuation; however, this should be determined by the surgeon or dentist. Benefits and risks of stopping warfarin should be assessed when making this decision.

Apixaban 48 hours prior to surgery or invasive procedures with a risk of major bleeding, and 24 hours before procedures with a risk of minor bleeding. The ESC and EHRA recommend resuming Apixaban 6 to 8 hours after the procedure. If the bleeding risk is severe, wait 48 to 72 hours after the procedure and use a low molecular weight heparin in the interim.

**ELIQUIP**

Eliquis (apixaban) is FDA approved for systemic embolism and stroke prophylaxis in non-valvular AF. It inhibits Factor Xa and thrombin; this interrupts the clotting cascade and decreases thrombin production. The inhibition of Factor Xa is reversible and selective and does not discriminate between free Factor Xa and Factor Xa bound to plasmas.

The manufacturer recommends taking a missed dose as soon as possible on the same day. Doses should never be doubled to compensate for a missed dose. The ESC and European Heart Rhythm Association (EHRA) recommendation is more specific and states that the missed dose can be taken up to 6 hours after it was scheduled. Once the 6-hour point has passed, the next dose should be taken at its scheduled time.

Laboratory monitoring is not necessary with Apixaban; however, as for warfarin, patients should monitor for signs and symptoms of major and clinically relevant non-major bleeding. Major bleeds include gastrointestinal, intracranial, intramuscular and cutaneous bleeding. Monitoring renal function is recommended due to the need for renal dose adjustments. Other side effects include hypersensitivity reactions and syncope.

There is no antidote for apixaban; although activated charcoal may be used in an overdose situation to reduce absorption. Charcoal administered at 2 hours after ingestion reduced Cmax by 27% and at 6 hours, charcoal reduced Cmax by 50%. Management of non-life-threatening bleeding consists of standard measures to include fresh frozen plasma. Limited data is available for proper management of a life-threatening bleed. Febriles, or PCI with activated Factor VIIa, has been studied in vitro and may be more beneficial than PCI alone. Fresh frozen plasma does not seem to correct the bleeding but may assist with plasma expansion in patients with large volume loss. More studies are needed to find a dependable antidote.

Clinical trials are underway for a possible Factor Xa inhibitor reversal agent.

Apixaban does not interact with vitamin K containing foods. However, it interacts with inhibitors and inducers of CYP450 3A4/5 liver enzymes and P-glycoprotein transporters. Apixaban should not be used with strong CYP3A4 and P-gp inhibitors such as ketoconazole or ritonavir due to increased concentration of apixaban and possible increased risk for bleeding. Strong CYP450 3A4 inducers such as rifampin, phenytoin, and St. John's Wort may decrease concentration and efficacy of apixaban.

Use of apixaban in ablation and cardioversion is still undergoing investigation; the data has yet to be published.

The manufacturer recommends discontinuing apixaban 48 hours prior to surgery or invasive procedures with a risk of major bleeding, and 24 hours before procedures with a risk of minor bleeding. The ESC and EHRA recommend resuming Apixaban 6 to 8 hours after the procedure. If the bleeding risk is severe, wait 48 to 72 hours after the procedure and use a low molecular weight heparin in the interim.
When restarting rivaroxaban, recommendations from the ESC and EHRA are similar to instructions for apixaban.10

**PRADAXA**

Pradaxa (dabigatran) is the only direct-thrombin inhibitor currently approved in the United States. Dabigatran is FDA indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular AF.

Patients should be instructed to store dabigatran in the original container to ensure potency due to moisture sensitivity.10,13

The missed dose should be taken as soon as possible on the same day if it is at least 6 hours before the next scheduled dose. Otherwise, the missed dose should be skipped and resumed at the next scheduled time.10,11

Peak plasma levels (C₀) are reached 2 hours after administration.10,15

No laboratory monitoring is needed to measure the anticoagulant effect of dabigatran. Monitoring for bleeding and renal function is recommended across the new oral anticoagulants.

The risk of bleeding and dyepepsia (due to the tartaric acid component in dabigatran) are the most common adverse effects. There is currently no antidote for bleeding, similar to the other new anticoagulants. Unlike the factor Xa inhibitors, hemodialysis may be an option for dabigatran removal although evidence is limited.11 Otherwise, management would be similar to that of the factor Xa inhibitors.

Dabigatran is affected by both P-gp inducers and inhibitors. Strong inducers like rifampin should be avoided due to possible decrease in dabigatran efficacy. The P-gp inhibitors dexamethasone and ketoconazole may require dose adjustment.13

There are no recommendations from the manufacturer for dabigatran in patients requiring an ablation.10 A few studies have suggested similar protocols for holding one dose of dabigatran the morning of the procedure (not recommended by manufacturer), using heparin during the procedure, and resuming either dabigatran that same evening or instituting bridging therapy with injectable anticoagulants. The safety and efficacy of this protocol compared to uninterrupted warfarin therapy varied among the studies.10

In the RE-LY trial when using dabigatran prior to cardioversion, there seemed to be comparable stroke rates to other anticoagulants based on observational data.10 Dabigatran is also mentioned as an option in guidelines.5

The manufacturer recommends discontinuing dabigatran 1 to 2 days prior to the procedure for patients with normal renal function. The recommended interval is increased to 3 to 5 days for patients with CrCl <50 ml/min. An increased interval may be considered for major invasive procedures.17

Other recommendations provide more specific times for dabigatran discontinuation based on procedure risk and renal function.10

**CONVERTING BETWEEN THERAPIES**

It may be necessary to convert a patient from one anticoagulant to another due to compliance, monitoring issues or side effects.

When converting from aspirin or Plavix to a new oral anticoagulant, dabigatran, rivaroxaban, or apixaban may be started immediately after the discontinuation of aspirin or Plavix.10 (see Converting between Therapies table)

There are additional recommendations for the three new oral anticoagulants (i.e., dabigatran, rivaroxaban or apixaban) to warfarin conversion.

Per the ESC and EHRA, both the new oral anticoagulant and warfarin may be used together until the INR is within the goal range. The new oral anticoagulant may increase the INR, so careful monitoring is recommended. Test the INR before the next new oral anticoagulant dose during concurrent use and again 24 hours after the last dose of the new oral anticoagulant is given. Continue to monitor the INR at regular intervals over the next month.10

**EFFICACY AND SAFETY**

Below is a summary of trials comparing individual new oral anticoagulants to warfarin for prevention of stroke and systemic embolism.

<table>
<thead>
<tr>
<th>Study trial</th>
<th>Efficacy compared to warfarin</th>
<th>Safety compared to warfarin</th>
<th>Study population</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ARISTOTLE</strong> (apixaban to warfarin)</td>
<td>Apixaban non-inferior (HR 0.79; 95 percent CI 0.66-0.95; p &lt; 0.001)</td>
<td>Apixaban fewer Intracranial and major bleeding, other types of bleeding</td>
<td>Average CHADS2 score=2.1²</td>
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<tr>
<td></td>
<td>Apixaban superior for intention to treat (ITT) population (p = 0.01)²</td>
<td>Rate of death lower in apixaban (p = 0.047)²</td>
<td></td>
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<tr>
<td><strong>RE-LY</strong> (dabigatran to warfarin)</td>
<td>Dabigatran 110 mg and 150 mg BID doses both non-inferior</td>
<td>GI bleeding most frequent dabigatran 150 mg BID dose</td>
<td>Average CHADS2 score=2.1²</td>
</tr>
<tr>
<td></td>
<td>Dabigatran 150 mg BID dose superior (RR 0.65; 95 percent CI 0.52-0.81; p &lt; 0.001)²</td>
<td>No significant difference major bleeding</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dabigatran 110 mg BID dose fewer rates major bleeding²</td>
<td><strong>ROCKET AF</strong> (rivaroxaban to warfarin)</td>
<td>Rivaroxaban non-inferior (HR 0.88; 95 percent CI 0.75-1.03; p &lt; 0.001)²</td>
</tr>
<tr>
<td></td>
<td>Rivaroxaban less frequent fatal and intracranial bleeding²</td>
<td>Average CHADS2 score=3.5²</td>
<td></td>
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</tbody>
</table>
ALL 3:
The results of ARISTOTLE, RE-LY and ROCKET AF were analyzed in an adjusted indirect comparison study. Since the average CHADS2 score and risk for stroke was higher in the ROCKET AF trial, two different analyses were conducted: 1) apixaban and dabigatran, and 2) the two anticoagulants in patients with a CHADS2 score greater than or equal to 3.19

The first comparison showed no significant difference in prevention of an event between apixaban and dabigatran; however, there was a 30 percent reduction in major bleeding with apixaban.19

The second comparison showed apixaban and dabigatran decreased the rate for an event by 20 percent when compared to rivaroxaban; however, this reduction was not statistically significant. Apixaban had a significantly lower rate of major bleeding than dabigatran and rivaroxaban.19

The CHADS2 scores and the inclusion/exclusion criteria were varied somewhat between the 3 studies. Further head-to-head trials are needed before a conclusion can be drawn as to the most effective and safest anticoagulant.19

CONCLUSION
As a result of the approval of several new oral agents, there are now several options for stroke prevention with AF in addition to warfarin, each with its own risks and benefits.

With regards to efficacy compared to warfarin, the new oral agents are non-inferior (rivaroxaban) or superior (apixaban, dabigatran) for stroke prevention in AF. With regards to safety compared to warfarin, major bleeding risk was less common with apixaban, more GI bleeding occurred with dabigatran but with similar rates of major bleeding, and similar major bleeding rates with rivaroxaban.

Ultimately, the choice of anticoagulant will depend on individual patient characteristics, goals, and preferences to maximize adherence and efficacy while maintaining safety.

References


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# CONVERTING BETWEEN THERAPIES

<table>
<thead>
<tr>
<th>Drug</th>
<th>Conversion between therapies</th>
<th>Dose adjustments</th>
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<tbody>
<tr>
<td>Warfarin</td>
<td>To dabigatran or apixaban:</td>
<td>Per PT/INR monitoring</td>
</tr>
<tr>
<td></td>
<td>When INR below 2, stop warfarin and start new agent</td>
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<td></td>
<td>To rivaroxaban:</td>
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<tr>
<td></td>
<td>Xarelto (rivaroxaban) package insert specifically states stop warfarin when</td>
<td></td>
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<tr>
<td></td>
<td>INR below 3 and start rivaroxaban(^{[0,15]})</td>
<td></td>
</tr>
<tr>
<td>Pradaxa (dabigatran)</td>
<td>To rivaroxaban or apixaban:(^{[10]})</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stop dabigatran and start new agent when next dose is due(^{*})</td>
<td></td>
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<td></td>
<td></td>
<td>Normal renal function:</td>
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<tr>
<td></td>
<td>To warfarin:</td>
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<tr>
<td></td>
<td>CrCl (\geq50) mL/min stop dabigatran 3 days after starting warfarin</td>
<td>150 mg BID</td>
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<td>CrCl 30-50 mL/min stop dabigatran 2 days after starting warfarin</td>
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<td></td>
<td>CrCl 15-30 mL/min, stop dabigatran 1 day after starting warfarin</td>
<td>75 mg BID</td>
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<td></td>
<td>CrCl &lt;15 mL/min, no recommendation available</td>
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<tr>
<td></td>
<td>Monitor INR throughout, INR more accurate 2 days after last dose of dabigatran(^{18})</td>
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<tr>
<td>Xarelto (rivaroxaban)</td>
<td>To dabigatran or apixaban:(^{[19]})</td>
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<tr>
<td></td>
<td>Stop rivaroxaban, start new agent when next dose is due(^{*})</td>
<td></td>
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<tr>
<td></td>
<td>To warfarin:</td>
<td></td>
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<tr>
<td></td>
<td>Stop rivaroxaban and start warfarin with bridge therapy when next dose is due(^{12,17})</td>
<td>20 mg qday</td>
</tr>
<tr>
<td>Eliquis (apixaban)</td>
<td>To dabigatran or rivaroxaban:(^{[10]})</td>
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<tr>
<td></td>
<td>Stop apixaban and start new agent when next dose is due(^{*})</td>
<td></td>
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<tr>
<td></td>
<td>To warfarin:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stop apixaban and start warfarin with bridge therapy when next dose is due(^{12,17})</td>
<td>5 mg BID</td>
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</tbody>
</table>

\(^{*}\)The exception is when higher plasma concentrations of the new oral anticoagulants are present, such as with renal dysfunction.\(^{10}\)

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