Newer Oral Anticoagulants Should Be Used as First-Line Agents to Prevent Thromboembolism in Patients With Atrial Fibrillation and Risk Factors for Stroke or Thromboembolism

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Newer Oral Anticoagulants Should Be Used as First-Line Agents to Prevent Thromboembolism in Patients With Atrial Fibrillation and Risk Factors for Stroke or Thromboembolism

Christopher B. Granger, MD; Luciana V. Armaganijan, MD

The incidence of atrial fibrillation (AF) appears to be increasing, even after adjustment for aging of the population. One in 4 people is projected to develop AF in his or her lifetime. Patients with AF have a 5-fold increased risk of stroke, and it is estimated that 15% to 20% of all strokes are attributable to AF. Moreover, death and disability from stroke complicating AF are particularly high. Thus, stroke related to AF is a substantial and growing public health burden.

Warfarin results in a two-thirds reduction in stroke on the basis of a meta-analysis of the randomized controlled trials (Figure). However, warfarin is grossly underused. In a relatively healthy insured population, ≈55% of eligible patients with AF received warfarin, and the rates dropped off substantially in the elderly, who have the greatest need. This low proportion of use and even greater underuse in higher-risk patients have been consistent findings across a number of US and European registries. In addition, not only is warfarin underused, but when it is used, it is used suboptimally. An inception cohort of elderly patients started on warfarin found that 28% of patients had discontinued warfarin by 1 year. Rates of major bleeding were very high, at >20% for patients with CHADS$_2$ (an acronym for congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and prior stroke or transient ischemic attack) score ≥4, during the first year, illustrating the vulnerability of patients on warfarin during initiation. International normalized ratios (INRs) were in the target range of 2.0 to 3.0 only 58% of the time. Reasons for underuse of warfarin and inability to consistently achieve target INR, at least in part, relate to pharmacological properties of the drug, including unpredictable anticoagulant effects, genetic variability in metabolism, multiple drug and food interactions, a narrow therapeutic window, and the resulting need for inconvenient monitoring. A large body of evidence shows a strong relationship of time in therapeutic range and risk of stroke, with an overview of 37 studies showing a 1% absolute annual increased risk of stroke for every 10% decrease in time in therapeutic range. Registries, often performed in settings with better than typical quality of warfarin use, have reported time in therapeutic range ≈50% of the time and worse results in elderly populations. A recent large trial database with higher-quality average INR has shown the same relationship of worse INR control and higher rates of stroke. Of interest, even with excellent INR...
control, hemorrhagic stroke rates were high, showing that warfarin has a liability of hemorrhagic stroke that might not be overcome with excellent INR control.

Antiplatelet therapy provides an estimated 22% relative risk reduction in stroke compared with control,4 and clopidogrel in addition to aspirin provides a 28% further relative risk reduction13 (Figure) but at a cost of bleeding comparable to that of warfarin.14

In summary, in general practice, warfarin has 2 major limitations: it is underused, and even when it is used, its use is suboptimal. Although some of the gaps in warfarin prescribings might be overcome by better systems of care, it is naive to think that warfarin will ever be a drug that can fulfill the enormous unmet medical need that now exists. We will present the case that the new oral anticoagulants provide major advantages to warfarin that should make them first-line agents to prevent thromboembolism in patients with AF and risk factors for stroke.

**New Direct Oral Anticoagulants for AF**

Several oral drugs directly inhibiting either coagulation factor II (thrombin) or factor Xa have been developed as alternatives to warfarin for stroke prevention in AF. The oral direct thrombin inhibitor ximelagatran was the first new oral anticoagulant to be compared with warfarin for prevention of thromboembolism in AF.14,15 Even though there was evidence of benefit, in at least 1 of the trials, we will not discuss it further because it was abandoned as a result of liver toxicity. We will concentrate on agents that have reported results from large randomized clinical trials. Table 1 compares and contrasts characteristics of warfarin with the factor II inhibitor dabigatran and the factor Xa inhibitors rivaroxaban, apixaban, and edoxaban. The Figure shows the effect of various antithrombotic therapies on stroke, with the use of an arbitrary scale of 10 for no therapy. Table 2 shows the effect of the new agents versus warfarin on major clinical outcomes.

**Dabigatran Eteoxilate**

Dabigatran etoxilate is a small-molecule direct thrombin inhibitor that is now approved in North America, Europe, and elsewhere for prevention of stroke in AF. Dabigatran etoxilate is hydrolyzed to the active moiety dabigatran, with maximum activity ~1 hour after administration. Its bioavailability is <10%, it is 80% renally metabolized, and its half-life is in the range of 12 to 17 hours. It has been developed to be administered twice daily.16,17

The Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial, a noninferiority randomized trial with open-label warfarin that included 18 113 patients with AF and at least 1 risk factor for stroke, demonstrated that dabigatran is safe and effective compared with warfarin. Warfarin was used with an INR target of 2.0 to 3.0, which was achieved 64% of the time in the trial. Two doses of dabigatran (110 and 150 mg twice daily) were studied. Dabigatran 150 mg was superior to warfarin in reducing the incidence of stroke (including hemorrhagic) and systemic embolism by 34% (P<0.001) with no significant difference in major bleeding. Dabigatran 110 mg was noninferior to warfarin in preventing stroke and systemic embolism and was associated with a 20% relative risk reduction in major bleeding compared with warfarin (P=0.003). Gastrointestinal bleeding was more common with higher-dose dabigatran than warfarin, and dyspepsia was more common with dabigatran (11.8% of patients with 110 mg and 11.3% of patients with 150 mg compared with 5.8% with warfarin; P<0.001 for both).18

**Rivaroxaban**

Rivaroxaban is a small-molecule oral direct inhibitor of factor Xa with high bioavailability, approximately one third renal metabolism, a half-life of ~9 to 12 hours, and peak plasma concentration 2.5 to 4 hours after dosing.19

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) was a double-blind, randomized comparison of rivaroxaban 20 mg once daily (with dose adjustment for renal function) versus dose-adjusted warfarin (INR target between 2.0 and 3.0, which was achieved a median of 58% of the time). The trial targeted high-risk patients with a...
CHADS<sub>2</sub> score of ≥2, and approximately half had history of prior stroke. There was a 12% relative risk reduction in the occurrence of stroke and systemic embolism in AF patients treated with rivaroxaban that did not reach statistical significance but was clearly noninferior to warfarin. Similar to dabigatran, there were significant reductions in intracranial hemorrhage, as well as in bleeding causing death.20

### Apixaban
Apixaban is an oral direct factor Xa inhibitor with a half-life of ≈12 hours and was developed for AF with twice-daily administration. Metabolism is 25% renal, and bioavailability is high. Similar to rivaroxaban, cytochrome P450 3A4 is involved with the metabolism so that strong inhibitors substantially increase drug levels.21

Two large randomized, double-blind trials have been conducted with apixaban for stroke prevention in AF: the Apixaban Versus Acetylsalicylic Acid to Prevent Strokes (AVERROES) and the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trials. AVERROES compared the efficacy of apixaban 5 mg twice daily with aspirin (81–325 mg once daily) for stroke and systemic embolism prevention in 5599 AF patients considered unsuitable for vitamin K antagonist treatment. The trial was stopped early on recommendation by the Data and Safety Monitoring Board because of clear benefits in regard to stroke reduction favoring apixaban (hazard ratio, 0.46; 95% confidence interval, 0.33–0.64; P=0.001). Strikingly, apixaban was associated with rates of major bleeding similar to those observed with aspirin.22 Apixaban was better tolerated than aspirin, with significantly fewer study drug discontinuations. The ARISTOTLE trial compared apixaban with warfarin for the prevention of stroke and systemic embolism in patients with AF and at least 1 additional risk factor for stroke.23 Compared with warfarin, apixaban reduced stroke and systemic embolism by 21% (P=0.01), resulted in 31% less bleeding (P<0.001), and resulted in 11% lower mortality (P=0.047). Apixaban was better tolerated than warfarin, with fewer drug discontinuations.

### Edoxaban
Edoxaban is an oral, small-molecule direct inhibitor of factor Xa that reaches maximum plasma concentration 1 to 2 hours after administration and has a half-life of 8 to 10 hours. Approximately 40% of elimination is renal.24 The Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation (ENGAGE AF-TIMI 48) trial has randomized >20 000 patients who have AF and a CHADS<sub>2</sub> score of ≥2. Patients were randomized in a double-blind fashion to warfarin (target INR, 2.0–3.0) or 1 of 2 doses of edoxaban given once daily,25 with dose adjustments both at baseline and subsequently for factors associated with higher drug exposure, including renal insufficiency. Results are expected in 2012.

### What Would It Take for New Direct Agents To Be First Choice?
Any drug has a combination of good and bad effects, and oral anticoagulants are no exception. The limitations of warfarin are well established. However, warfarin is highly effective when used optimally, is well established and accepted, and is inexpensive (although the monitoring and adverse reactions are an enormous burden to the healthcare system and to many patients). To take over as first choice for most patients, new anticoagulants must not only be more convenient (a key advantage that may also increase adherence and persistence) but also need to result

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**Table 1. Comparison of Pharmacological Characteristics of Warfarin and the New Oral Anticoagulants for Atrial Fibrillation**

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administration</td>
<td>Once a day</td>
<td>Twice a day</td>
<td>Once a day</td>
<td>Twice a day</td>
<td>Once a day</td>
</tr>
<tr>
<td>Target</td>
<td>Vitamin K-dependent factors</td>
<td>Factor II</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
</tr>
<tr>
<td>Time to peak effect</td>
<td>3–5 d</td>
<td>1 h</td>
<td>2.5–4 h</td>
<td>3 h</td>
<td>1–2 h</td>
</tr>
<tr>
<td>Dose</td>
<td>Variable</td>
<td>150 mg twice a day and 110 mg twice a day</td>
<td>20 mg every day (15 mg every day for renal impairment)</td>
<td>5 mg twice a day (2.5 mg twice a day for high risk)</td>
<td>30 mg every day and 60 mg every day (with adjustment for high exposure)</td>
</tr>
<tr>
<td>Half-life</td>
<td>40 h</td>
<td>12–14 h</td>
<td>7–11 h</td>
<td>12 h</td>
<td>9–11 h</td>
</tr>
<tr>
<td>Interactions</td>
<td>Multiple</td>
<td>Inhibitors of P-glycoprotein transporter*</td>
<td>Inhibitors of CYP 3A4 and P-glycoprotein transporter†</td>
<td>Inhibitors of CYP 3A4 and P-glycoprotein transporter†</td>
<td>Inhibitors of CYP 3A4 and prostaglandin transporter†</td>
</tr>
<tr>
<td>Renal clearance, %</td>
<td>0</td>
<td>80</td>
<td>35</td>
<td>25</td>
<td>40</td>
</tr>
<tr>
<td>Anticoagulation monitoring</td>
<td>Required</td>
<td>Not required</td>
<td>Not required</td>
<td>Not required</td>
<td>Not required</td>
</tr>
<tr>
<td>Antidote</td>
<td>Vitamin K</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

*Inhibitors of P-glycoprotein transporter include amiodarone (cautions with interaction) and verapamil.
†Inhibitors of CYP 3A4 and P-glycoprotein transporter include antifungals and protease inhibitors.
in better clinical outcomes, at an acceptable cost, with consistency in all major subgroups of patients. Do the new oral anticoagulants rise to this high standard?

**Convenience**

The new oral anticoagulants are far more convenient than warfarin because they have predictable pharmacodynamic effects and, at doses tested in the large trials, have good efficacy and safety profiles without anticoagulation monitoring. They avoid the need for frequent dose adjustment that may contribute to dosing errors. Dabigatran and apixaban are administered twice a day. Rivaroxaban and edoxaban are given once a day. All of the new agents have the advantage of rapid onset of action and relatively short half-life periods, making their use around the time of procedures more convenient than warfarin, without the need for bridging.

**Efficacy Outcomes**

The Figure shows that all 3 new anticoagulants are at least as good as warfarin at preventing stroke, and because warfarin itself is very effective, the benefit compared with no therapy is a major one. Table 2 shows that 2 agents (dabigatran 150 mg twice daily and apixaban 5 mg twice daily) are more effective than warfarin in terms of preventing stroke. All 3 result in a 10% reduction in mortality, although this reached statistical significance only for apixaban.

**Safety Outcomes**

Even more remarkable than the superior efficacy, the rate of hemorrhagic stroke was reduced by 40% to 70% and that of intracranial hemorrhage by 50% with all 3 of the agents, suggesting a liability to warfarin in regard to intracranial hemorrhage. Both lower-dose dabigatran and apixaban re-
sulted in important reductions in major bleeding. These important benefits in clinical outcomes provide the most compelling rationale for their use as first-line agents.

Patients Already on Warfarin and With Good INR Control
Some have suggested that although the new agents provide important benefits for patients not previously on warfarin, there is little advantage to switching if patients are tolerating warfarin with good INR control. Although on the surface this conclusion seems rational, it is not supported by the data. The benefits of the new anticoagulants were similar regardless of prior use of warfarin.\textsuperscript{18,20,23,26} With dabigatran, there was no statistically significant evidence of less benefit of stroke prevention in centers with better INR control.\textsuperscript{12} Importantly, the benefit of dabigatran over warfarin in reducing intracranial hemorrhage appeared to be nearly identical across INR control ranges.\textsuperscript{12} The pattern of a consistent benefit regardless of INR control appears to be the case for rivaroxaban and apixaban as well.

Effect on Mortality
As shown in Table 2, all 3 new anticoagulants result in an \approx 10\% reduction in mortality, although this reached statistical significance only for apixaban. This is not surprising given the striking reduction in hemorrhagic stroke and underscores the important advantages of all 3 new anticoagulants. Although the new agents have some limitations, such as no reversal agent in the event of bleeding, the fact that mortality tends to be lower suggests that, overall, the clinical benefits clearly outweigh the risks.

Lack of Specific Antidotes
The safety of the new drugs has been challenged because there is no reversal agent. Although this is true, surprisingly little is known about the effectiveness and time course of reversal of warfarin with vitamin K. The new agents have an important feature that leads to reversibility, that of a relatively short half-life. Despite the lack of a specific antidote, bleeding was both less common and less severe, at least with lower-dose dabigatran and apixaban. All 3 agents substantially reduce the most serious type of bleeding, intracranial hemorrhage, and its consequences.

Is the Cost Acceptable?
Expense of the new agents will be a limiting factor for many patients, in both the United States, where much of the burden will be on the individual patient, and in other countries that may have more constraints on healthcare spending. However, at least the first agent to be approved, dabigatran, appears to be cost-effective in the US healthcare system.\textsuperscript{27} Cost-effectiveness calculations depend on whether one believes that the dabigatran effect is modified by the quality of warfarin treatment on the basis of time in therapeutic INR range,\textsuperscript{28} for which there is no statistically significant evidence.\textsuperscript{12} Information on cost-effectiveness of the other agents awaits their arrival on the market and detailed analyses.

Conclusion
Although warfarin has been a highly effective treatment to reduce stroke in AF, its limitations are well known by physicians and patients. New oral anticoagulants have been shown to be convenient and to have important advantages in improving clinical outcomes, including fewer strokes, less intracranial hemorrhage, and lower mortality. These benefits are consistent whether or not patients have been on warfarin previously. Moreover, the cost appears to be acceptable, particularly in light of the major advantage with regard to convenience. Thus, the newer agents should generally be used as first-line treatment for stroke prevention in AF.

Disclosures
Dr Granger reports the following: research grants from Bristol-Myers Squibb and Pfizer (\$10 000) and Boehringer Ingelheim (\$10 000); Boehringer Ingelheim (\$10 000); honoraria from Bristol-Myers Squibb and Pfizer (\$10 000); and consultant/advisory board for Bristol-Myers Squibb and Pfizer (\$10 000). Dr Armaganijan reports no disclosures.

References


Response to Granger and Armaganijan

Jack Ansell, MD

Granger and Armaganijan recite the findings from the large atrial fibrillation trials showing varying degrees of efficacy and safety of new agents compared with warfarin, and state, “The limitations of warfarin are well established.” That is precisely the point of this debate: The limitations of warfarin are well established, but the limitations of new agents are not.

As an example, investigators assumed that they knew the limitations of ximelagatran, an earlier direct thrombin inhibitor. Liver toxicity occurred in 6% to 10% of patients with long-term, not short-term, therapy, but real-world experience in Europe showed that even short-term therapy was not without its risks of important liver toxicity. The drug has since been shelved.

In the last 4 months, 3 countries (Japan, Australia, and New Zealand) have expressed concern or issued warnings to physicians about an inordinate number of major bleeding episodes occurring in patients with atrial fibrillation treated with a new direct thrombin inhibitor, and the manufacturer has just recently agreed to recommend monitoring of kidney function to patients taking the drug in Europe. It is unknown whether these anecdotal reports represent a rate higher than that seen in the clinical trials, and it will require phase 4 postmarketing studies or registries to help to clarify the situation. Whether or not the consequences of poor drug adherence will result in a higher rate of ischemic stroke remains to be seen, but this is also a concern.

The problems of warfarin therapy leading to suboptimal treatment or underuse are well known, but greater focus on improving warfarin management by more widespread anticoagulation management services and much greater use of patient home monitoring, the latter of which has shown results as good as if not better than the best care provided by an anticoagulation service, are needed.