Emerging Therapy Critiques

Apixaban in Atrial Fibrillation
From Bleeding Cows to 21st Century Medicinal Chemistry

Brett L. Cucchiara, MD; Scott E. Kasner, MD

It is hard to imagine a poorer candidate drug than warfarin. It has a narrow therapeutic window, multiple interactions with other drugs, and a multitude of dietary interactions. It has unpredictable dose–response characteristics mandating trial-and-error dose adjustment and requires frequent blood monitoring to achieve therapeutic levels and avoid toxicity. Consequently, many patients are unable or unwilling to be treated with warfarin. Further, those patients that can be treated with warfarin spend just over half the time actually within the therapeutic target range of the drug.1 And yet, for more than 50 years, warfarin and the other vitamin K antagonist derivatives (VKAs) have been the only available oral anticoagulants. Were it not for the extraordinary efficacy of these medications at preventing stroke and other thromboembolic events, such drugs could not possibly have survived in clinical use so long.

The discovery of the VKAs has its roots in the environmental degradation of the midwestern United States in the 1920s.2 During the so-called “Dust Bowl” years, depletion of soil nutrients due to poor farming practices led to dramatic changes in local ecosystems. It was soon found that sweet clover could survive in the barren soil, and coincident with the spread of sweet clover came a hemorrhagic disease in cattle. Two veterinarians, Drs Schofield and Roderick, determined that the hemorrhagic disease was due to consumption of moldy sweet clover and that the disease was associated with a reduction in prothrombin activity. The (possibly apocryphal) story of the discovery of the VKAs themselves occurred in 1933, when a farmer in Wisconsin, upset by this hemorrhagic disease killing his cattle, brought a pail of unclotted blood to Dr Karl Link at the University of Wisconsin in Madison.2 Over the next 8 years, Dr Link was able to isolate and identify the causative agent in sweet clover, and dicumarol, the first VKA, was synthesized and given its name by early 1941. Within several months, investigators at the Mayo Clinic had given dicumarol to 6 patients and published their preliminary results. Probably never again will a compound move from the “bench to bedside” with such speed!

Decades later, advances in pharmacogenetics finally identified part of the problem with VKAs. Common variants in genes involved in the metabolism of these drugs dramatically influence an individual’s dose requirement. Despite this important observation, clinical trials have yet to demonstrate that genetic-based dosing algorithms improve time in the therapeutic range or clinical outcomes, and there is substantial doubt as to whether such an approach could be cost-effective.3

Meanwhile, it has taken approximately 70 years for the next generation of oral anticoagulants to emerge from clinical development. However, finally, these new oral anticoagulants are indeed emerging. Within just the past 5 years, several large Phase III trials of new oral anticoagulants in patients with atrial fibrillation have either been completed or are nearing completion, and other agents are in early clinical development. These agents include the oral direct thrombin inhibitor dabigatran (the first agent to achieve regulatory approval in the United States) and the oral factor Xa inhibitors rivaroxaban, apixaban, edoxaban, and betrixaban. The oral direct thrombin inhibitor ximelagatran showed efficacy similar to warfarin in 2 large trials but was abandoned due to liver toxicity.4,5 The development pathway of these drugs has varied, but the case of apixaban (the subject of this article) is instructive. Unlike the serendipitous discovery of warfarin, the development of apixaban exemplified modern rational drug design, combining focused screening of compounds with chemical structures suggestive of potential activity at the biological target (Factor Xa), iterative chemical modifications to optimize the structure–activity relationship using x-ray crystallography and computer modeling, and further chemical engineering to achieve the desired oral bioavailability and pharmacokinetics.6

The new oral anticoagulants all share notable advantages over the VKAs, including predictable anticoagulant effects at fixed doses, limited drug and food interactions, no need for routine blood level monitoring, and a broader therapeutic window. The consistent anticoagulant effect achieved with these agents may also translate into greater efficacy and safety due to avoidance of the frequent sub- and supratherapeutic drug levels which are common with VKA therapy. Indeed, in the Randomized Evaluation of Long-term anticoagulation therapY (RE-LY) trial, 150 mg dabigatran twice daily showed a substantial advantage over warfarin in reducing stroke and systemic embolism (relative risk reduction,
The pharmacological properties of these new drugs have the potential to greatly expand the number of patients eligible for oral anticoagulant therapy. One obvious population that might benefit is those patients with atrial fibrillation unable or unwilling to use warfarin. In this population, the current standard treatment approach is to use aspirin. Randomized trials have shown that aspirin in this setting is much less effective than warfarin although more effective than placebo. Combining aspirin with clopidogrel modestly improves efficacy over aspirin alone, although at the cost of substantially increased bleeding, but is markedly inferior to warfarin.

**Apixaban in Patients With Atrial Fibrillation Ineligible for Warfarin: The AVERROES Trial**

The AVERROES trial was a double-blind, randomized, controlled trial comparing the oral Factor Xa inhibitor apixaban with aspirin in subjects with atrial fibrillation who were not candidates for warfarin therapy. To be eligible, subjects had to be ≥50 years of age, have atrial fibrillation, and have ≥1 of the following: prior stroke or transient ischemic attack, age ≥75 years, hypertension, diabetes, heart failure, or peripheral arterial disease. Subjects had to be ineligible for VKA therapy either because of previous inability to use VKAs or expected inability to use VKAs in the future. The major reason for ineligibility for VKAs in the trial was concern about ability to monitor and adjust VKA therapy appropriately. For approximately 15% of the patients, the sole reason for ineligibility was patient refusal to take a VKA, and for 11%, the sole reason was that the patient’s embolic risk (as estimated by a CHADS$_2$ score of 1) was deemed too low to justify VKA therapy. Approximately half (52%) had multiple reasons for not taking VKAs.

Subjects were randomized to either 5 mg apixaban twice daily or aspirin at a dose of 81 to 324 mg daily. The choice of aspirin dose was at the discretion of the local investigator. A small percentage of subjects (approximately 7%) were randomized to a reduced apixaban dose of 2.5 mg twice daily. This lower dose was used in subjects who met 2 of the following criteria: age ≥80 years, body weight ≥60 kg, or serum creatinine ≥1.5 mg/dL. The primary efficacy outcome of the trial was the occurrence of stroke (either ischemic or hemorrhagic) or systemic embolism, and the primary safety outcome was the occurrence of major bleeding. Secondary outcomes included rates of myocardial infarction, vascular death, all-cause mortality, and composites of major vascular events.

A total of 5599 patients were enrolled and randomized, and the mean follow-up period was 1.1 years. The study was terminated early by the Data Safety Monitoring Board based on a prespecified interim analysis showing clear superiority of apixaban. The primary efficacy outcome was significantly lower in the apixaban-treated compared with the aspirin-treated group (1.6% per year versus 3.7% per year; hazard ratio, 0.45; 95% CI, 0.32 to 0.62; P<0.001). Rates of major bleeding were similar between the 2 groups (1.4% per year with apixaban, 1.2% with aspirin; hazard ratio, 1.13; 95% CI, 0.74 to 1.75; P=0.57). Subgroup analyses showed effects consistent with the overall trial, both in terms of efficacy and bleeding risk, across all major analyzed subgroups. The absolute benefit of apixaban over aspirin was magnified in the subgroup of patients with prior stroke or transient ischemic attack due to an elevated overall rate of stroke or systemic embolism in this group.

**Implications of AVERROES**

The AVERROES trial demonstrated that Factor Xa inhibition with apixaban is substantially better than aspirin at preventing embolic events in patients with atrial fibrillation. The relative benefit of apixaban over aspirin (relative reduction in hazard 55%) is comparable to that seen in a meta-analysis of trials comparing adjusted-dose warfarin with aspirin (relative risk reduction, 38%), indirectly suggesting that apixaban is likely to be at least as effective an oral anticoagulant as warfarin. One notable finding in AVERROES was the extremely low bleeding rate with apixaban, which was comparable to that seen with aspirin. This finding has important implications because, if true, it suggests that a much broader range of patients with atrial fibrillation, including those at low risk of stroke, might be better treated with apixaban than aspirin. But should we believe this finding, and if so, does this indicate something particular about apixaban compared with other oral anticoagulants? First, although there is a widespread perception that the risk of major hemorrhage is dramatically higher with warfarin than aspirin in patients with atrial fibrillation, this is not entirely supported by the data. In a recent meta-analysis of 8 studies comparing dose-adjusted warfarin with aspirin, the absolute excess risk of intracranial hemorrhage with warfarin was 0.2%/year and the excess risk of major extracranial hemorrhage was also 0.2%/year. Thus, the overall excess bleeding risk was approximately 0.4%/year with warfarin compared with aspirin. This difference is well within the 95% CI of the differential bleeding risk between apixaban and aspirin seen in AVERROES. Furthermore, in an on-treatment analysis in AVERROES, the differential bleeding risk between apixaban and aspirin was somewhat magnified (1.4% per year with apixaban, 0.9% with aspirin; hazard ratio, 1.54; 95% CI, 0.96 to 2.45; P=0.07). Compared with other trials of antithrombotic therapy in atrial fibrillation in the past decade, the bleeding rates seen in AVERROES in both treatment groups were low, with aspirin being somewhat less effective than apixaban.

Regarding this latter point, for instance, in AVERROES approximately 9% of patients in both the apixaban and aspirin groups received nonstudy aspirin for more than half of the trial period, compared with the RE-LY trial in which approximately 20% of patients were on aspirin continuously throughout the trial. Use of aspirin combined with oral anticoagulation has been clearly associated with an increased bleeding risk. At present, the seemingly low bleeding risk with apixaban must be considered with appropriate skepticism.
Table. Rates of Major Bleeding in Large, Randomized Trials of Antithrombotic Therapy in Atrial Fibrillation Performed in the Past Decade*

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Rate of Major Bleeding per Year, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAFTA</td>
<td>2.0 1.9</td>
</tr>
<tr>
<td>ACTIVE-A</td>
<td>1.3 2.0</td>
</tr>
<tr>
<td>ACTIVE-W</td>
<td>2.2 2.4</td>
</tr>
<tr>
<td>SPORTIF-III</td>
<td>2.2 1.5</td>
</tr>
<tr>
<td>SPORTIF-V</td>
<td>3.5 2.7</td>
</tr>
<tr>
<td>RE-LY</td>
<td>3.6 3.3</td>
</tr>
<tr>
<td>ROCKET-AF</td>
<td>3.5 3.6</td>
</tr>
<tr>
<td>AVERROES</td>
<td>1.2 1.4</td>
</tr>
</tbody>
</table>

ASA indicates aspirin; BAFTA, Birmingham Atrial Fibrillation Treatment of the Aged Study; ACTIVE, Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events; SPORTIF, Stroke Prevention Trial Using an Oral Thrombin Inhibitor in Atrial Fibrillation; RE-LY, Randomized Evaluation of Long-term anticoagulation therapy; ROCKET-AF, Rivaroxaban—Once-daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation.

*Data shown from the RE-LY trial are for the 150-mg twice-daily dose of dabigatran.

What Comes Next?
The remaining question is how apixaban compares to warfarin when compared head to head. This question is being addressed by a large Phase III randomized trial (Apixaban for Reduction In STroke and Other Thromboembolic Events in atrial fibrillation [ARISTOTLE]) directly comparing apixaban with warfarin in 18,000 patients with atrial fibrillation. Preliminary results announced in a press release in June 2011 indicated that apixaban was superior to warfarin in terms of both efficacy and major bleeding, but no quantitative data have yet been presented. The full report of ARISTOTLE is eagerly awaited.

After many years of wrestling with the difficulties of warfarin, it seems quite likely that clinicians will soon have an embarrassment of riches in new-generation oral anticoagulants for atrial fibrillation. Dabigatran has already received regulatory approval in the United States and elsewhere and has rapidly entered clinical practice. Rivaroxaban appears likely to achieve regulatory approval in the near term based on the results of 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) trial. In the event that ARISTOTLE shows apixaban comparing favorably to warfarin, there will be 3 new oral anticoagulants available in clinical practice to replace warfarin. If that comes to pass, we will be entering a new era of debate on the comparative efficacy and safety of these agents.

Disclosures
B.C. has received honoraria from Boehringer-Ingelheim for lectures. S.K. has received payment from Pfizer for serving on a blinded endpoint adjudication committee for trials not related to anticoagulants or atrial fibrillation.

References

Key Words: apixaban • atrial fibrillation • embolic stroke • oral anticoagulation • warfarin
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