New Oral Anticoagulants Should Not Be Used as First-Line Agents to Prevent Thromboembolism in Patients With Atrial Fibrillation

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

New Oral Anticoagulants Should Not Be Used as First-Line Agents to Prevent Thromboembolism in Patients With Atrial Fibrillation

Jack Ansell, MD

When Karl Paul Link, in 1939, isolated the substance derived from spoiled sweet clover that was the causative agent of hemorrhagic disease of cattle,¹ it is unlikely that he would have imagined that the vitamin K antagonists (VKA) would be around 70 years later and would be used to prevent arterial and venous thromboembolism in 1% to 2% of the world population of developed countries. The longevity of a drug, even one with as many perceived drawbacks as warfarin, the primary vitamin K antagonist, says something about this agent. How many drugs can be listed as consistently reducing by two thirds the incidence of a devastating consequence of a pathological cardiac rhythm? Yet, great fanfare has attended the introduction of the new oral anticoagulants as agents to replace warfarin. Entire pages of The New York Times are devoted to direct-to-consumer advertisements, multiple satellite symposia are conducted at professional meetings, and frequent reviews appear in medical journals singing their praises. But just how good are these agents, and should they be used as first-line therapy for stroke prevention in atrial fibrillation (AF)? Let us briefly examine the data.

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Dabigatran etexilate, an oral direct thrombin inhibitor, when dosed at 150 mg twice daily in the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial, produced a significant reduction in stroke or systemic embolism compared with warfarin in selected patients with nonvalvular AF (1.11% versus 1.69%; relative risk, 0.66; 95% confidence interval [CI], 0.53–0.82; P<0.001 for superiority) with a similar incidence of major bleeding (3.11% versus 3.36%; relative risk, 0.93; 95% CI, 0.81–1.07; P=0.003 for superiority). Rivaroxaban, an oral direct factor Xa inhibitor, was shown to be noninferior to warfarin for the prevention of stroke or systemic embolism in patients with nonvalvular AF 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) trial (2.12% versus 2.42%; hazard ratio, 0.88; 95% CI, 0.74–1.03; \( P=0.117 \)) and was similarly noninferior with respect to major bleeding (3.6% versus 3.45%; hazard ratio, 1.04; 95% CI, 0.90–1.20; \( P=0.576 \)). These apparently beneficial results were predicted several years earlier by the oral direct thrombin inhibitor ximelagatran, which proved to be noninferior to warfarin for stroke prevention in AF and for major bleeding. However, the hepatic toxicity of this drug, which initially was believed to be a minor and controllable side effect of long-term therapy, proved to occur even with short-term therapy, the drug was removed from the market, and further development ceased.

These are the top-line results from the recent trials, and, without knowing more, it is understandable that physicians would be eager to change the paradigm of AF therapy from a VKA to a direct factor inhibitor, especially because these agents are touted as requiring no coagulation monitoring and thus may be more convenient. However, it is important to delve further into the results of these trials to see what else the data tell us. Both the RE-LY and ROCKET-AF trials had important inclusion/exclusion criteria that limit their ability to be generalized or at least raise questions in regard to how well they will perform in the real world of nonselected AF patients. In the RE-LY trial, warfarin was given and managed in an open-label format, introducing the potential for biased management. The RE-LY trial had a 21% dropout rate in the dabigatran group versus 17% in the warfarin group; a significant increase in dyspepsia in the dabigatran group versus warfarin (\( \simeq 12\% \) versus \( 6\% \)); an unexplained increase in acute myocardial infarction in the dabigatran group versus warfarin; a significant increase in major gastrointestinal bleeding compared with warfarin, although within the context of a noninferior or lower overall major bleed rate; and, most importantly, a vanishing difference in relative efficacy as the management of warfarin improved, as determined by the time in therapeutic range (Table 1). Many of the details of the ROCKET-AF trial are unknown because the results have not been fully published, but from the initial presentation, we learn that the management of warfarin (median time in therapeutic range 57.8%, with 20% of time below an international normalized ratio [INR] of 2) was less than ideal (Table 2).

The last of the published phase III AF trials, the Apixaban Versus Acetylsalicylic Acid to Prevent Strokes (AVERROES) trial, compared apixaban, another oral direct factor Xa inhibitor, with aspirin in patients whose physicians thought they were not candidates for warfarin or for other reasons did not want to use warfarin. Apixaban showed a significant reduction in stroke or systemic embolism compared with aspirin without causing an increase in major bleeding, and the trial was stopped prematurely. However, the trial has been criticized on many fronts, most importantly for the casual and unsystematic criteria applied by physicians for not using warfarin in these patients. AVERROES essentially recapitulated the much earlier trials of warfarin versus aspirin, in which warfarin showed a further 37% reduction in stroke or systemic embolism compared with aspirin. How well apixaban will compare with warfarin will soon be available with the results of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial.

Even if these new agents prove to be no better than warfarin in the long run, they are still touted as favorable agents because of their predictable anticoagulant response, absence of food interactions, and limited drug interactions compared with warfarin. As a result, monitoring of anticoagulant effect is said not to be needed, making drug management potentially easier than with warfarin. The half-life periods of these agents are also shorter than that of warfarin, in the range of 8 to 17 hours for the various agents, allowing for a rapid decline of drug level and anticoagulant effect compared with warfarin, a potential benefit if major bleeding

Table 1. Rates of Stroke and Systemic Embolism of Dabigatran Compared With Different Levels of Warfarin Therapeutic Control as Determined by Time in Therapeutic INR Range. RE-LY Rates of Stroke and Systemic Embolism per 100 Person-Years (Hazard Ratio, 95% Confidence Interval vs Warfarin)\(^9\)

<table>
<thead>
<tr>
<th>INR Time in Therapeutic Range, %</th>
<th>Dabigatran 110 mg Twice a Day</th>
<th>Dabigatran 150 mg Twice a Day</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;57.1</td>
<td>1.91</td>
<td>1.10</td>
<td>1.92</td>
</tr>
<tr>
<td>57.1–65.5</td>
<td>1.00 (0.68–1.45)</td>
<td>0.57 (0.37–0.88)</td>
<td></td>
</tr>
<tr>
<td>65.5–72.6</td>
<td>0.81 (0.56–1.17)</td>
<td>0.50 (0.33–0.77)</td>
<td></td>
</tr>
<tr>
<td>&gt;72.6</td>
<td>0.89 (0.58–1.36)</td>
<td>0.69 (0.44–1.09)</td>
<td></td>
</tr>
<tr>
<td>1.18</td>
<td>1.23</td>
<td>1.27</td>
<td>1.34</td>
</tr>
<tr>
<td>1.04 (0.61–1.48)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

INR indicates international normalized ratio; RE-LY, Randomized Evaluation of Long-Term Anticoagulant Therapy.

Table 2. Rates of Stroke and Systemic Embolism of Rivaroxaban Compared With Different Levels of Warfarin Therapeutic Control as Determined by Time in Therapeutic INR Range. ROCKET-AF Rates of Stroke and Systemic Embolism per 100 Person-Years (Hazard Ratio, 95% Confidence Interval vs Warfarin)\(^9\)

<table>
<thead>
<tr>
<th>INR Time in Therapeutic Range, %</th>
<th>Rivaroxaban</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–50.6</td>
<td>1.8</td>
<td>2.5</td>
</tr>
<tr>
<td>0.71 (0.48–1.03)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50.7–58.5</td>
<td>1.9</td>
<td>2.2</td>
</tr>
<tr>
<td>0.83 (0.62–1.29)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>58.6–65.7</td>
<td>1.9</td>
<td>2.1</td>
</tr>
<tr>
<td>0.92 (0.62–1.28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>65.7–100</td>
<td>1.3</td>
<td>1.8</td>
</tr>
<tr>
<td>0.77 (0.49–1.12)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

INR indicates international normalized ratio; 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.
was to occur. Finally, depending on the agent, the new agents have either renal or mixed renal/liver elimination/metabolism, allowing a clinician to choose a particular drug to meet the patients’ comorbid conditions. Embedded in these pharmacokinetic attributes, however, are some of the sources of major problems for these new agents.

Table 3 highlights many of the drawbacks of the new oral anticoagulants. How much of an impact these shortcomings will have on real-world outcomes remains to be seen, and that question is a major reason for clinicians to be restrained in their immediate use of these agents as front-line therapy for AF. The principal concern most often verbalized pertains to drug compliance or adherence. Because of their short half-life periods in combination with the fact that they do not require routine coagulation monitoring, the issue of medication adherence becomes extremely important. Given the regimentation and follow-up that occur in clinical trials, adherence is seldom a problem, but medication adherence is a real concern in everyday medical treatment, leading to increased rates of morbidity, mortality, and, in turn, overall healthcare costs. The degree of adherence is influenced by many factors. Approximately 50% of patients across varying genders, ages, ethnicities, and medical disorders fail to follow their prescribed medication regimen. Cost, especially out-of-pocket costs, is a major factor affecting adherence. A recent survey questioned 700 physicians and found that their biggest concern was that patients were not filling their prescriptions or were skipping their pills because of financial stresses in order to make the prescriptions last longer. The estimated cost of one of the new agents already made 5 visits to a pharmacy over a 3-month period. Their study population with cardiovascular disease was elderly and not different from those who might be on an anticoagulant for AF. Median medical adherence in their study group was ≈67%.

Dose regimens also influence the degree of adherence. Claxton et al showed an ≈10% drop in adherence (starting from a baseline of 79%) for medications that are taken once daily versus twice daily. One of the new agents is taken twice daily for stroke prevention in AF, as is another currently under study.

Nuisance bleeding has also been shown to reduce adherence in patients taking aspirin alone versus clopidogrel. Only 1% of patients reported nonadherence in an aspirin group, rising to >11% for those taking clopidogrel in another study. Certainly, such nuisance bleeding occurs with both VKAs and new anticoagulants, but the short half-life of new agents makes nonadherence more likely to be dangerous.

Warfarin users are not immune to the problem of nonadherence. Waterman et al found that 36% of out-of-range INRs were due to nonadherence in a cohort of 347 patients studied over a year. In a prospective cohort study of 111 patients initiating warfarin, Platt et al found that warfarin nonadherence occurred on 21% of the patient days observed. Adherence was measured by “bottle openings”; 92% of patients missed at least 1 bottle opening, and 36% missed >20% of their bottle openings. Independent risk factors for nonadherence included education level, employment status, mental health functioning, and cognitive impairment. Investigators found a significant association between nonadherence and subtherapeutic INRs. These studies reflect the same patients who would be treated with a new short-acting anticoagulant. Although the studies of Platt et al and Waterman et al were underpowered to detect adverse events, given the short half-life periods of the new anticoagulants compared with warfarin, the potential for more sustained periods of subtherapeutic anticoagulation exists and may have a significant impact on efficacy. Warfarin has an average half-life of ≈36 hours, which is dependent on an individual’s CYP 2C9 genetic phenotype, as well as other factors such as other medications and liver disease. Because of the long offset of action, missing an occasional dose may not be a problem even if the INR falls transiently below therapeutic range.

The absence of significant symptoms until a stroke occurs in many patients with AF can also be a factor influencing drug compliance because patients may not fully understand the importance of their medication, as demonstrated in a recent survey. Anticoagulation management clinics are useful in monitoring and managing adherence, and they achieve high rates of time in therapeutic range. Such clinics are not likely to be involved in the management of patients on new oral anticoagulants.

The lack of a simple coagulation assay to accurately measure the biological effect of new agents is another...
concern.\textsuperscript{14} No need for routine monitoring may be a beneficial consequence of the predictable pharmacology of new agents, but the ability to accurately measure a drug effect when needed would be highly desirable. This becomes important in a variety of situations: Is the patient taking the drug if a stroke occurs? Is the patient excessively anticoagulated if a major bleed occurs? Is it safe to take a patient to emergent surgery if an accurate degree of anticoagulation cannot be measured? Although a variety of routine coagulation assays are recommended to assess drug effect, the correlation of drug effect and assay is poor, and the sensitivity of different reagent/instrument combinations is not at all established.\textsuperscript{33,34}

Although the new agents have limited drug interactions compared with the vitamin K antagonists, they are not totally free of such interactions. The serum concentration of several of the new agents is influenced by potent P-glycoprotein inhibitors or inducers, and some of the drugs are metabolized, in part, by the P450 cytochrome system in the liver (particularly CYP 3A4).\textsuperscript{35} Not knowing the full spectrum of such interactions and not having a monitoring assay to assess their impact further support the admonition that these agents should not be used as front-line therapy.

Because at least 1 of the new drugs is predominantly eliminated unchanged by the kidney and others have greater or lesser degrees of renal elimination, fluctuating renal function is another variable that must be considered carefully. Renal function declines with age but, more importantly, can fluctuate widely with comorbidities. Such volatility of renal function in the elderly can lead to varying drug levels and unknown consequences, leaving the physician unaware, especially without a readily available monitoring assay.

The ability to titrate and monitor drug effect is also desired by clinicians. The VKAs have a well-established range in balancing benefit versus risk, and extensive data exist to determine risk at the boundaries of that range as well as below and above the range.\textsuperscript{30,36,37} On the basis of an individual’s risk of thromboembolism and risk of bleeding, a clinician can target therapy with a VKA (personalized medicine) that will most benefit the individual. Perhaps it is better to have a monitored drug than an unmonitored drug.

Although a reduction in intracranial bleeding has been a consistent finding with at least 2 of the new agents, both are associated with an increase in gastrointestinal bleeding, a more common event in the elderly. How to specifically manage such bleeding with these agents is still unknown. Using an anticoagulant without a well-established means of reversal in the case of major or life-threatening hemorrhage or in preparation for emergent major surgery should make the clinician think twice about what he or she would do in this setting. The VKAs have several possible reversal agents that can be used for various degrees of urgency. Vitamin K will substantially reverse the level of anticoagulation over 12 to 24 hours.\textsuperscript{30} For more urgent situations, fresh frozen plasma, at appropriate doses, will reverse the degree of anticoagulation and bleeding risk in the short term (<12 hours), and for life-threatening bleeding, 3- or 4-factor prothrombin complex concentrates (vitamin K–dependent factors) will reverse the level of anticoagulation and bleeding within minutes.\textsuperscript{30,38–40} Presently, there are no specific antidotes for these new agents. Their short half-life periods are favorable attributes in non-urgent situations. In the setting of major or life-threatening bleeding, there are no established therapeutic procedures. Hemodialysis will reduce the concentration of 1 of the new agents\textsuperscript{41} but is not very practical in the setting of an acute intracerebral hemorrhage. Prothrombin complex concentrates and recombinant factor VIIa have been used anecdotally,\textsuperscript{34,42} but the physiological rationale in regard to why they should be effective is lacking, and the clinical evidence just does not exist. Until we better understand the means to reverse the anticoagulant effect or develop a specific antidote, we should use these agents with caution and restraint.

Drug cost is another factor that must be taken into consideration. Out-of-pocket expense for these new agents will be considerably more than for warfarin, and we have already commented on the manner in which this might affect drug adherence if patients are unwilling to make the copayment that might be required.\textsuperscript{32} Societal costs must also be taken into consideration whenever a new therapy is introduced. In a Markov decision model, Freeman et al\textsuperscript{43} computed quality-adjusted life-years, costs, and incremental cost-effectiveness ratios for dabigatran versus dose-adjusted warfarin therapy in patients with AF. They estimated total costs of $143 193 for warfarin versus $164 675 for low-dose dabigatran and $168 398 for high-dose dabigatran. The incremental cost-effectiveness ratios for low-dose and high-dose dabigatran compared with warfarin were $51 229 and $45 372, respectively. These borderline favorable ratios were all predicated on the outcomes achieved with 1 randomized trial, which, as we have already discussed, may not translate into real-world outcomes. With different outcomes, a similar analysis might result in dramatically different cost-effectiveness ratios. In another Markov analysis recently published, Shah and Gage,\textsuperscript{44} once again using outcomes achieved in the RE-LY trial, found that cost-effectiveness ratios depended on an individual patient’s risk of stroke and hemorrhage on warfarin. For those at the low end of the risk scale for both, aspirin was most cost-effective. For those with the highest risk of hemorrhage or stroke, dabigatran, 150 mg twice daily, was most cost-effective. The take-home message from these studies indicates that cost-effectiveness is highly dependent on patient characteristics as well as the outcomes attributed to each treatment modality, which, at the present time, we can only derive from 1 randomized controlled trial. For at least 1 new agent, out-of-bottle capsule stability may also be a factor with an impact on outcomes when used in the general population.\textsuperscript{45} The impact of this capsule characteristic should make clinicians cautious in their selection of patients, especially the elderly with multiple other medications that
must be identified and partitioned over the usual week’s course of therapy.

Finally, given all of these unknowns, do we know which patients will do best on these new drugs? What are the characteristics that make someone the optimal patient to start or transition to a new oral anticoagulant? Can these new agents replace the VKAs for all indications? They cannot if many of the indications have yet to be studied, such as patients with mechanical heart valves. Is the VKA patient with an unstable INR the ideal candidate to take a drug that does not require monitoring? That patient is not if the INR instability is due to poor compliance. Is the highly stable, uncomplicated VKA patient the ideal candidate? Why switch and risk a complication with a new drug in such a stable patient? Is the geographically isolated patient without access to laboratory INR monitoring the ideal candidate? Perhaps, but such an individual now has the opportunity to perform point-of-care INR monitoring at home. As recommended by the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, these factors and more need to be considered before patients are started on or switched to 1 of these new agents. 46

In summary, it cannot be denied that the new oral direct factor inhibitor anticoagulants offer pharmacokinetic characteristics of interest to patients and clinicians. However, there are enough unknowns at the present time to caution healthcare providers against the use of these agents as first-line therapy for patients with AF. Until we understand the impacts that various levels of drug nonadherence have on outcome, the appropriate assays to measure anticoagulant effect when needed, the means to manage major bleeding or drug overdose or drug reversal, and the characteristics of the appropriate patient candidate, these new agents should not automatically replace warfarin in patients with AF and should not be used as first-line therapy in patients with AF.

Disclosures

The author is a consultant for Bristol-Myers Squibb, Pfizer, Boehringer Ingelheim, Janssen, and Daiichi and serves on the Data Safety Monitoring Board of Bristol-Myers Squibb.

References

Response to Ansell

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

Dr Ansell has provided a thoughtful and useful perspective that focuses on many of the practical challenges with implementation of the new oral anticoagulants, including cost. However, rather than use these as reasons not to use the new agents, we believe that his concerns can and must be addressed and that doing so will enable an enormous benefit to patients.

His single largest concern regards adherence, about which he provides an excellent discussion. As he acknowledges, adherence to warfarin is poor, and thus there is an opportunity to improve adherence to oral anticoagulation with the new agents but only if the challenge is recognized and addressed. It is notable that adherence to apixaban was better than to aspirin, as least as reflected by permanent discontinuation, in the Apixaban Versus Acetylsalicylic Acid to Prevent Strokes (AVERROES) trial.

Although the level of anticoagulation with new agents can be assessed with available laboratory tests, more work needs to be done to guide clinicians on their use. Given the lack of specific antidotes, more data are needed on practical ways to manage bleeding with the new agents. However, this is not a reason to avoid their use, and, in fact, the best way to deal with bleeding is to avoid it, which is achieved with all of the new agents with regard to the most serious bleeding, intracranial hemorrhage. In the end, on the basis of several large trials, the new agents have important advantages over warfarin, including lower rates of stroke and much lower rates of intracranial hemorrhage, convenience, and lower mortality, and thus they should be first-line agents over warfarin.