

NOVEL ORAL ANTICOAGULANTS IN THE ELDERLY



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Abstract

Advanced age is one of the greatest risk factors for atrial fibrillation, and with it comes an increased risk of thromboembolic events. Three novel oral anticoagulants (apixaban, dabigatran, and rivaroxaban) are now available for use in patients with atrial fibrillation. While the efficacy of the agents has been established, long-term evidence and safety issues, especially in frail and elderly patients, continue to cause concern among practitioners.

In this article, the authors review the evidence regarding the novel oral anticoagulants in the elderly and highlight the risks and benefits of these agents compared with warfarin.

Résumé

L'âge avancé représente un des facteurs de risque les plus importants de fibrillation auriculaire (FA) et d'événements thrombo-emboliques associés. Trois nouveaux anticoagulants oraux (apixaban, dabigatran, rivaroxaban) peuvent maintenant être utilisés chez les patients avec FA. L'efficacité de ces agents est bien établie, mais les données quant à leurs bénéfices et sécurité à long terme, surtout chez les personnes âgées fragiles, représentent une source de préoccupation chez les cliniciens.

Dans cet article, les auteurs révisent les données probantes concernant ces nouveaux anticoagulants oraux chez les personnes âgées tout en soulignant leurs risques et bénéfices en comparaison à la warfarine.

For many years, warfarin has been the gold standard for anticoagulation in patients with atrial fibrillation. However, in 2010 the first new oral anticoagulant in over 60 years, dabigatran, became available for use in Canada. Since then, two other novel agents, rivaroxaban and apixaban, have come available. While the evidence for these agents is favourable, clinicians remain wary of their use, particularly in frail older patients.

Other than previous stroke, advanced age provides the single greatest risk for thromboembolic stroke in patients with atrial fibrillation. In fact, a Danish study¹ found that age over 75 was a greater risk factor for thromboembolism than hypertension, diabetes, or congestive heart failure. Given that almost 10% of people over 80 years of age have atrial fibrillation,² the elderly population is clearly at high risk.

For years, clinicians have had a challenging time dealing with warfarin and its many side effects. Concerns about monitoring international normalized ratios (INRs), bleeding, and drug-

drug interactions are of paramount consideration for a population of patients who are at risk of falls, who are on multiple medications, and for whom just getting to a laboratory for monitoring can be a challenge. Elderly patients with cognitive impairment are significantly more likely to have dangerously supratherapeutic INRs (>6) than are elderly patients without cognitive impairment.³ While the ability to monitor warfarin in patients with cognitive impairment can be useful, these patients are also at much higher risk of adverse events. One of the greatest concerns with warfarin is the risk of an intracranial bleed, as studies have shown that the risk of intracranial hemorrhage (ICH) in patients anticoagulated on warfarin increases with advancing age.⁴ Elderly patients have a baseline risk for ICH of 0.15% per year, and warfarin increases this risk to 0.3–0.8% per year. Another significant limitation of warfarin is the challenge of keeping the INR within a therapeutic range over a long period of time. Numerous recent studies show that *even* with optimal monitoring, the amount of time that patients have a

therapeutic INR ranges from 55–66%^{5,6}; another way to think of this is that these people are at sub- or supra-therapeutic levels 34–45% of the time. Finally, elderly patients are frequently on antibiotics, antifungals, thyroid hormone replacement therapy and amiodarone, drugs that, among others, can make keeping INR in the therapeutic range a significant challenge. Given the many concerns with warfarin, it is important to evaluate the new agents with this in mind: is there evidence that the new agents are safer and/or more efficacious at preventing ischemic stroke in the older population?

The first question that must be answered is whether these agents have been sufficiently studied for use in the frail elderly. Three major trials, RE-LY,⁷ ROCKET,⁵ and ARISTOTLE,⁶ had a mean age of participants of 71, 70, and 73 years, respectively. In ROCKET, 31% of participants were over the age of 75 years, while in ARISTOTLE, 25% of patients were over 78. All three trials used appropriate populations that are reflective of typical atrial fibrillation patients that physicians see in practice, including those with multiple medical co-morbidities. The results were impressive. Apixaban showed a 21% reduction in the rate of thrombotic stroke when compared with warfarin, while reducing the rate of a clinically significant bleed by 31%.⁶ Both rivaroxaban and dabigatran showed non-inferiority to warfarin when comparing the rate of thromboembolic stroke, and dabigatran, similar to apixaban, had significantly fewer major hemorrhages.^{5,7}

While there are valid concerns with regard to the novel agents, the overarching worries about bleeding and the lack of a reversal agent may be somewhat unfounded. While bleeding from any location is a concern, most bleeds can be managed with transfusions and supportive care while the anticoagulant clears from the blood. In general, the half-life of the novel agents is approximately 12 hours (dabigatran 12–17 hours,⁸ rivaroxaban 5–13 hours,⁹ and apixaban 12 hours¹⁰); however, with low glomerular filtrations rates, the half-life of these agents can be significantly prolonged. Intracranial bleeds provide the greatest concern for clinicians and patients alike, due to the devastating outcomes that may ensue. Here, a review of the evidence is useful to put these events into context. Averaged, the new oral anticoagulants reduce the rate of hemorrhagic stroke by 53% compared with warfarin.¹¹ Furthermore, it is unclear whether hemorrhagic strokes on warfarin are less devastating than those on the novel agents because of warfarin's reversibility – a recent study showed that while the INR of patients on warfarin with an intracranial bleed could be rapidly reversed, the morbidity and mortality

remained high.¹² In a post hoc analysis of the RE-LY study, patients with an intracranial bleed on dabigatran had a statistically better survival rate and spent less time in the intensive care unit, showing a trend toward a better prognosis than in patients on warfarin.¹³ If we can reduce intracranial bleeds by over 50% in the first place, perhaps the lack of a reversal agent is less of a concern than we think.

As a group, all three oral anticoagulants have shown efficacy at least comparable to that of warfarin in their ability to prevent embolic strokes.¹⁴ Each agent, however, has different pharmacokinetic and pharmacodynamic profiles. By targeting different elements in the coagulation cascade, each drug comes with its own potential drug interactions and rates of adverse events. Dabigatran, for example, has been associated with significantly more gastrointestinal bleeding than warfarin, an outcome not seen with apixaban and not recorded in the rivaroxaban trial.^{5–7}

There are no easy answers for elderly patients with atrial fibrillation. Many clinicians are unfamiliar with the new agents and feel that they are more comfortable with a tried-and-tested warfarin regimen. Dabigatran is contraindicated in patients with renal failure or who have declining glomerular filtration rates, and this has led to restrictions for its use in elderly patients with chronic kidney disease. Other concerns include a lack of long-term data and the significant purchasing cost. These medications certainly carry potential side effects, and we are still discovering their long-term safety profile; for example, a recent meta-analysis showed an increase in the rates of acute coronary events in patients taking dabigatran compared with warfarin.¹⁵ Furthermore, just deciding which agent to use can be a challenge as no study to date has done a head-to-head comparison of the novel agents. These concerns are certainly valid, and in patients in whom warfarin has been easily managed without concern, making the switch to a new agent may not be beneficial.

There is strong evidence, however, that used in the right patient, the novel oral anticoagulants may prove significantly safer and easier to use in our elderly population than we initially thought. While the long-term evidence is still incomplete, the initial trials of novel anticoagulants are proving, study by study, that these agents are viable options for elderly patients.

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Key Points

- Novel oral anticoagulants have been studied in the elderly population.
- Other than a previous stroke, in patients with atrial fibrillation, advanced age is the greatest risk factor for a thromboembolic stroke.
- Averaged, the three novel oral anticoagulants reduced rates of intracranial hemorrhage by 53% compared with warfarin.
- While there is a paucity of long-term safety data, initial studies and experience show that the novel oral anticoagulants are safe when used in carefully selected elderly patients.

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