

Stroke prevention in older adults with atrial fibrillation

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See related research article by Xu and colleagues in *CMAJ Open* at www.cmajopen.ca/content/1/3/E115

The new oral anticoagulants dabigatran, rivaroxaban and apixaban are approved in more than 80 countries for stroke prevention in patients with atrial fibrillation. These medications offer simplification of long-term oral anticoagulation because, unlike vitamin K antagonists, they do not require routine coagulation monitoring or dietary restrictions. Moreover, in phase III trials of their use in atrial fibrillation, the new oral anticoagulants reduced the risk of intracranial bleeding by 30%–70% compared with warfarin and were at least as effective as warfarin in preventing ischemic stroke.¹ On the basis of these findings, guidelines recommend new oral anticoagulants in preference to vitamin K antagonists in most patients with atrial fibrillation.^{2,3}

In an article published in *CMAJ Open*, Xu and colleagues present an evaluation of prescribing patterns of oral anticoagulants in the province of Ontario, Canada, since the approval of dabigatran, the first new oral anticoagulant to become available in Canada for stroke prevention in atrial fibrillation.⁴ Over the 24-month study period from October 2010 to September 2012, prescriptions for new oral anticoagulants in the province rose steadily, with a corresponding decline in prescriptions for warfarin. By the end of the study period, new oral anticoagulants represented 21% of all prescriptions for oral anticoagulants. Age-specific prescribing rates of dabigatran were highest among older patients, and more than 90% of prescriptions for dabigatran among patients 85 years or older were for the lower dosage (110 mg twice daily).

Xu and colleagues are concerned that older patients were not adequately represented in the randomized controlled trials of new oral anticoagulants for stroke prevention in atrial fibrillation and conclude that there is an urgent need to evaluate outcomes in clinical practice.⁴ Are their concerns justified?

Population data indicate that atrial fibrillation affects 1%–2% of the general population and that the prevalence of atrial fibrillation and burden of related stroke rise sharply with age.⁵ The median age of patients with atrial fibrillation is 75 years, and the condition affects 10% of patients over the age of 80.⁵ One-sixth of all strokes are cardio-

embolic, a rate that rises to almost one-third among patients over 80.⁵ Strokes in patients with atrial fibrillation are associated with greater morbidity and mortality than strokes in those without atrial fibrillation. Nevertheless, vitamin K antagonists are consistently underused in older patients, with the most common barriers being concerns about inconvenience and risk of bleeding.⁶

The simplicity of treatment with new oral anticoagulants makes them particularly attractive as an alternative to warfarin in older patients, but do the efficacy and safety results from randomized controlled trials of new oral anticoagulants also apply to older patients in clinical practice?

Three completed phase III trials compared a new oral anticoagulant with warfarin in patients with atrial fibrillation. These randomized controlled trials collectively included 19 100 patients with atrial fibrillation who were 75 years or older, which is more than the total number of patients included in prior trials comparing warfarin with placebo or untreated control ($n = 2900$) or comparing warfarin with acetylsalicylic acid ($n = 4620$).^{1,7} Although the absolute risk of stroke and bleeding is substantially higher among older patients than among younger patients, the relative effects of new oral anticoagulants compared with

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KEY POINTS

- Older patients with atrial fibrillation have a higher risk of stroke and worse outcomes after stroke than younger patients, but many do not receive recommended anticoagulation treatment.
- Subgroup analyses of data for more than 19 100 patients aged 75 years or older enrolled in phase III trials suggest that the new oral anticoagulants dabigatran, rivaroxaban and apixaban offer consistent benefits over warfarin in older patients with atrial fibrillation.
- The rate of intracranial bleeding, the most feared complication of anticoagulation, is related to age and is sharply reduced by the new anticoagulants relative to warfarin, making these agents particularly attractive for older patients.
- Uptake of new oral anticoagulants in Canada has been rapid. Their use in older patients is consistent with guideline recommendations and is supported by the results of clinical trials.
- Ongoing surveillance by regulatory authorities and postmarketing studies of the use of new oral anticoagulants will help to inform uptake of the medications and related outcomes among older patients in clinical settings.

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control were consistent for the primary efficacy outcome of stroke or systemic embolism in all 3 trials and for major bleeding in the ROCKET-AF and ARISTOTLE trials.¹

A significant interaction between age and treatment was evident for major bleeding in the RE-LY trial. Among patients 75 years or older ($n = 7258$), 150 mg of dabigatran twice daily was associated with a borderline significant increase in major bleeding, and 110 mg twice daily with a similar rate of major bleeding, compared with warfarin. Among patients less than 75 years of age, both doses were associated with a reduction in major bleeding.¹ The increase in major bleeding with the higher dose of dabigatran in the older patients was confined to extracranial bleeding; both doses of dabigatran were associated with lower rates of intracranial bleeding irrespective of age. Furthermore, the results obtained with dabigatran for both total stroke and intracranial bleeding were consistent among patients 80 years or older ($n = 3016$) and those 85 or older ($n = 720$).⁸ These findings would appear to support recommendations by Canadian, European and Australian regulators for preferential use of the lower dose of dabigatran in patients 75 years or older. Regulators in the United States did not approve the lower dosage of 110 mg twice daily, reasoning that there was no population (including older patients) for whom the availability of a lower dose would improve dabigatran's benefit–risk profile.

A postmarketing report from the US Food and Drug Administration and the results of a Danish nationwide study provide additional reassurance about the safety of new oral anticoagulants in the general population.^{9,10} Both reports are subject to confounding because of their observational design, but they provide no evidence that bleeding rates experienced to date with dabigatran are any higher in the real world than those reported in the randomized controlled trials.

Guideline panels have long highlighted the underuse of anticoagulants for stroke prevention in patients with atrial fibrillation. Regulatory approval of 3 new oral anticoagulants holds the promise that a greater proportion of patients with atrial fibrillation at risk for stroke will receive effective preventive therapy. We believe that the findings of Xu and colleagues of increasing use of new oral anticoagulants among Canadians with atrial fibrillation are encouraging and that the pattern of uptake of these agents is supported by the data from the randomized trials. We agree, however, that there is no room for complacency, because anticoagulants can cause serious bleeding and the risk of complications is increased when new oral anticoagulants are not used according to approved indications. Translation of the favourable

results of the trials into benefits for patients requires clinicians to prescribe new oral anticoagulants for the right patient and at the right dose, with appropriate follow-up and periodic monitoring of renal function (e.g., at least once per year and more often in the presence of moderate impairment).

Ongoing surveillance by regulatory agencies and evidence from large-scale international post-marketing studies such as GLORIA-AF (www.gloria-af.com) and GARFIELD (www.tri-london.ac.uk/garfield) should help to inform the future uptake of new oral anticoagulants and related outcomes in real world settings.

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