Well-managed warfarin is superior to NOACs

I read with interest the articles on the new oral anticoagulants (NOACs)—dabigatran, rivaroxaban, and apixaban—in the November issue of *Canadian Family Physician*.[1,2] Although the articles ably detail the nuances of NOAC use in clinical practice, they ignore some very significant facts.

Limitations of the NOAC randomized controlled trial (RCT) evidence base. The multinational NOAC RCTs demonstrated noninferiority to warfarin at and below the following mean international normalized ratio (INR) time in therapeutic range (TTR): 64% for dabigatran in the RELY (Randomized Evaluation of Long-term Anticoagulation Therapy) trial[3]; 55% for rivaroxaban in the 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) trial[4]; and 62% for apixaban in the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial.[5] There is no statistically significant RCT evidence to support the noninferiority of the NOACs over well-managed warfarin at a mean TTR greater than 64%.

Well-controlled or well-managed warfarin. Well-controlled or well-managed warfarin (TTR > 64%) can be easily achieved by primary care physicians, other health professionals, and patients when they are provided with the right tools. For example, in Canada, the Stollery Children's Hospital in Edmonton, Alta,[6] operates a warfarin therapy self-management program for patients. The mean TTR for the program's patients is 87%; average age among patients is 12 years old. Sweden's national Web-based atrial fibrillation (AF) registry (AuriculA)[7] assists in warfarin dosing and tracks TTRs, tightness of INR control, and adverse events. In 2008, Sweden's mean TTR was 76.2% overall. The primary care portion was 80.3%.[7]

Canadian Cardiovascular Society guidelines. In the absence of noninferiority at a TTR greater than 64%, the evidence-based application of the Canadian Cardiovascular Society guidelines should be limited to patients who cannot achieve a TTR greater than 64%. The reader might ask, "How can my patients measure their TTR?" Calculating TTR by the Rosendaal et al[8] method is a complicated 4-step calculation. Until now, there has been no easy way for patients or physicians to measure TTR without computer software. And because we predominantly use manual warfarin-dosing systems in Canada, we have been unable to measure TTR.

But here is the good news: there is an app for patients called *INR log*.[9] This app was developed by INR Online and it will track your patients' INRs, warfarin doses, and dates of INR tests; the app reminds users about their upcoming INR tests, graphs INR results, calculates TTR, and provides an audit trail of their warfarin doses, INR results, and compliance with INR testing. This tool will allow you to identify patients whose TTR is greater than 64% and should not be switched to an NOAC, as well as those whose TTR is less than 65% and should be considered for an NOAC.

Warfarin as first-line treatment for AF. From the foregoing, it follows that warfarin should be used as the first-line oral anticoagulant in most patients to see if they can achieve a TTR greater than 64%. Not every patient can be well-managed by using warfarin, but a large percentage of patients can be. To initiate the NOACs without allowing these potentially well-managed patients to be identified or switching

well-managed patients from warfarin to an NOAC is a disservice to our patients and to our health care system. Improved TTRs translate into fewer strokes and hemorrhages and lower health care costs.

The need to improve warfarin management in Canada. Like our non–family physician specialist colleagues, family physicians are not happy with the "standard care model" of warfarin management. It is inefficient and provides suboptimal INR control. We need government-funded access to better tools to provide optimal warfarin management. What are these proven tools?

- Computer software that is capable of dosing warfarin and measuring TTR must replace the manual warfarin-dosing system.[10] In addition, we need a single warfarin database in Canada as part of a national AF registry similar to Sweden's.
- Point-of-care INR testing must replace laboratory INR testing in most instances. Testing options need to be widened to provide patients with improved access and convenience. In New Zealand, the Community Pharmacy Anti-coagulation Management Service study achieved a mean TTR of 78.6% overall and 80.3% after 6 months.[11]
- Patient self-management systems should use point-of-care INR testing in a structured program taught by diabetes or anticoagulation educators and be supervised by family physicians. Such programs have existed in Germany for 25 years; their TTRs average greater than 80% (Dr Stephan Kress, oral communication, September 2014). Patients in these programs are tested weekly. There are 200 000 German patients who self-manage. Patients who are unable to self-manage warfarin dosing usually have caregivers who are trained to assist them. We need to train caregivers.
- Use of 1-mg warfarin tablets in most cases instead of our 9 different warfarin strengths might simplify warfarin dosing, avoid tablet confusion, and permit daily or weekly dose adjustments of 0.5 mg. In Germany, patients in the self-management programs use 1-mg tablets only (Dr Stephan Kress, oral communication, September 2014).

To implement the use of these tools in Canada, we need government funding for the following elements:

- computer software ($24 per patient per annum)[12];
- point-of-care INR strips ($7 per strip)[13] and devices ($375 per device)[14]; and
- patient training by diabetes or anticoagulant educators (4 hours per patient) (Dr Stephan Kress, oral communication, September 2014).

The total cost, including monitoring and the warfarin drug, is half the cost of the NOACs and provides TTRs greater than 70%, further reducing strokes, hemorrhages, and their associated costs to a level unattainable by NOACs. Finally, in addition with warfarin, we can now cheaply monitor the degree of anticoagulation and compliance (INR) plus the quality of warfarin management (TTR), and we can affordably and promptly reverse warfarin in the event of major or minor bleeding.

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Competing interests
Dr Trusler is Vice President of INR Online Canada Limited, a not-for-profit Canadian company dedicated to the improvement of warfarin management in Canada.

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Response

We thank Dr Trusler for his interest in our articles,[1,2] but we disagree with his claim that we "ignored some very significant facts" pertaining to a comparison of the efficacy and safety of new oral anticoagulants (NOACs) with warfarin for stroke prevention in patients with atrial fibrillation (AF).

The objective of our articles[1,2] was not to compare NOACs with warfarin, which has been comprehensively reviewed elsewhere.[3,4] Instead, we specifically explained the following:

> [T]his review focuses on treating patients who are currently taking NOACs and does not consider the process for choosing an appropriate anticoagulant for