This is a revised version of the article published in the October 2014 issue (BCMJ 2014;56:391-394). The author corrected an error that appeared in Table 1 in the original article (edoxaban 60 mg was in the ENGAGE trial, not the RE-LY trial).

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It's time to pull the plug on the new oral anticoagulants for nonvalvular atrial fibrillation

Studies comparing dabigatran and similar agents with warfarin do not demonstrate noninferiority when warfarin is properly managed.

ABSTRACT: The new oral anticoagulants studied in trials designed to demonstrate noninferiority to warfarin (RE-LY, Rocket-AF, Aristotle, and ENGAGE) are used in fixed-dose regimens while warfarin is a variable-dosing drug. Therefore, any meaningful comparison of warfarin with such agents must account for the quality of warfarin management as measured by the average time in therapeutic range for the international normalized ratio (INR) and the tightness of INR control (i.e., the closeness of INR values to the target INR). Because of differences in the quality of warfarin management, the findings for intracranial hemorrhage and hemorrhagic stroke in these multinational studies do not reflect Canadian clinical experience, and therefore should not be used to support the use of new oral anticoagulants for nonvalvular atrial fibrillation. This position was stated clearly in a 2011 *Therapeutics Letter*, and the issue now needs to be addressed by Health Canada, the Canadian Cardiovascular Society, and the Canadian Agency for Drugs and Technologies in Health.

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Three new oral anticoagulants (NOACs) are now on the market in Canada for use in patients with nonvalvular atrial fibrillation. The agents are dabigatran, rivaroxaban, and apixaban. Standing in the wings awaiting Health Canada approval is edoxaban. (While the term target-specific oral anticoagulants, or TSOACs, is also used for these agents, we will use the more familiar term NOACs in this article.)

The randomized controlled trials supporting the use of these agents in Canada are RE-LY (dabigatran 110 mg and 150 mg),[1] Rocket-AF (rivaroxaban),[2] Aristotle (apixaban),[3] and ENGAGE (edoxaban 30 mg and 60 mg).[4] All four studies used stroke or systemic embolism as the primary outcome and were designed to demonstrate that each NOAC is noninferior to warfarin. However, while NOACs are used in fixed-dose regimens, warfarin is a variable-dosing drug requiring careful management. Therefore, any meaningful comparison of warfarin and other agents must account for the quality of warfarin management. This is measured by the average time in therapeutic range (TTR) for the international normalized ratio (INR) and the tightness of INR control (the closeness of INR values to the target INR). The closer INR values are to the target INR, the fewer outliers, resulting in strokes and hemorrhages, will be experienced. When discussing warfarin performance, references to warfarin are meaningless unless properly referenced in the context of time in therapeutic range and tightness of INR control.

To illustrate these points, let us look first at ischemic strokes and TTR in the RE-LY trial.[1] The study's mean TTR was 64%. At this TTR, subjects taking dabigatran 110 mg experienced 159 ischemic strokes, those taking dabigatran 150 mg experienced 111 ischemic strokes, and those taking warfarin experienced 142 strokes. But, when using the RE-LY data in a sensitivity analysis at TTRs great-

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Any meaningful comparison of warfarin and other agents must account for the quality of warfarin management.

er than 72.6% (the upper quartile),[5] dabigatran 150 mg subjects experienced 35 ischemic strokes and warfarin subjects 29. Although the numbers are smaller and lack the same statistical significance, at this TTR range there is no evidence for claiming that dabigatran 150 mg is noninferior to warfarin with respect to the prevention of ischemic stroke. What is our mean TTR nationally in Canada? Nobody knows because computer software is required to calculate the TTR (Rosendaal method) and we primarily rely on manual warfarin dosing systems in Canada. Furthermore, in RE-LY the mean TTR for Canada was 71%, not 64%, the mean TTR for all 44 participating countries.

Secondly, let us look at the importance of the tightness of INR control in two trials. Sportif V, a trial comparing ximelagatran to warfarin,[6] with a mean TTR of 68%, had a hemorrhagic stroke rate of 0.1% in the warfarin control arm. ENGAGE, a trial comparing edoxaban to warfarin,[4] with a median TTR of 68% had a hemorrhagic stroke rate 9 times higher than that found in Sportif V at 0.9% in its warfarin control arm. How do we explain the difference? The exceptional feature of Sportif V was the tightness of INR control: 83% of the INR values in the study were between 1.8 and 3.2. Sportif V was carried out in North America and ENGAGE was carried out in 46 countries.

Clearly, the hemorrhagic stroke rates from multinational trials involving many countries (39 to 46) cannot be used to support NOAC use in Canada because of differences in the quality of our warfarin management systems. This difference in real-world warfarin management in Canada is further demonstrated by the intracranial hemorrhage (ICH) rates identified by Gomes and colleagues, who carried out a study at the Institute of Clinical and Evaluative Studies (ICES) at the University of Toronto to determine the rates of hemorrhage among Ontario patients treated with warfarin in routine clinical practice.[7] The large sample size of 125 195 subjects constituted almost half the patients on warfarin in Canada. The median age for starting warfarin therapy was 77 years. The subjects were real-world patients, and were treated according to Canadian, as opposed to international, warfarin management practices.

In **Table 1** the rate of ICH in the ICES study is compared with rates in the multinational NOAC trials (both treatment arms and the control arms). It is clear that the ICH rate in Ontario, at 0.20%, is lower than the ICH rates in the treatment and control arms of the NOAC multinational RCTs.

Table 1. Rate of intracranial hemorrhage in ICES, a real-world, Canadian population-based study of warfarin, versus rates in new oral anticoagulant and warfarin arms of multinational RCTs.

Trial	Drug	Number of subjects	Number of countries	Trial duration (years)	TTR (%)	ICH rate (%)
ICES	warfarin	125 195	1	5.0	—*	0.20
RE-LY	dabigatran 110 mg	6 015	44	2.0	64	0.23
ENGAGE	edoxaban 30 mg	7 034	46	2.8	68**	0.26
RE-LY	dabigatran 150 mg	6 076	44	2.0	64	0.30
Aristotle	apixaban	9 052	39	1.8	62	0.33
ENGAGE	edoxaban 60 mg	7 035	46	2.8	68	0.39
Rocket-AF	rivaroxaban	7 111	45	2.0	55	0.50
Rocket-AF	warfarin	7 125	45	2.0	55	0.70
RE-LY	warfarin	6 022	44	2.0	64	0.74
Aristotle	warfarin	9 088	39	1.8	62	0.80
ENGAGE	warfarin	7 036	46	2.8	68	0.85

TTR = time in therapeutic range
ICH = intracranial hemorrhage
* Measuring TTR (Rosendaal method) is a four-step mathematical equation best calculated by computer software. ICES did not have TTR data available for this study because, in Canada, we generally rely on manual warfarin dosing systems incapable of performing this calculation.
** ENGAGE investigators reported TTR as a median; all others in this table are means.

Although it is generally unacceptable to compare dissimilar studies, RCTs should by design result in findings that beat real-world experience. Dr Gomes explains these findings as follows: "Given that the studies with higher estimates consolidate data from many countries, it could be that variations in health care setting are leading to higher rates [of ICH] elsewhere (perhaps due to differences in monitoring, dose titration, etc.)" (personal communication by e-mail with T. Gomes, 17 December 2012).

Similar discrepancies can be seen in **Table 2**, where the rates of hemorrhagic stroke in the warfarin arms of the multinational RCTs are 7 to 9 times higher than the rate in the North American Sportif V trial.

It appears that hemorrhagic stroke rates are overstated in the warfarin arms of all the NOAC multinational trials for the Canadian context, and therefore so are the primary endpoints and the conclusions of noninferiority of NOACs to warfarin.

Thus, the NOAC RCTs are not valid in the Canadian context, and since there is no other RCT evidence of statistical significance to support NOAC use in Canada, these agents should be removed from the market by Health Canada for use in nonvalvular atrial fibrillation until such evidence from Canadian RCTs is available to justify their use.

Furthermore, there are other concerns that make caution desirable. The NOACs were brought to market without a reversal agent or a monitoring test that establishes patient adherence. As well, although the most efficacious NOAC in the prevention of ischemic stroke is dabigatran 150 mg, the RE-LY authors reported that dabigatran 150 mg had double the GI hemorrhage rate of warfarin at a TTR greater than 72.6%.[5] With no reversal agent, monitoring test, or bleeding management strategy, it is no wonder that dabigatran has been the subject of litigation related to GI hemorrhages in the US.[8]

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NOACs are also expensive (e.g., $1200 per year) and no cost has been attached yet to a future monitoring test or reversal agent. In the meantime, patients risk prolonged and expensive resuscitations for bleeding complications.

In 2011, the Therapeutics Initiative at the University of British Columbia boldly addressed deficiencies of the RE-LY trial.[9] In a *Therapeutics Letter* reviewed by 60 experts and primary care physicians, the Therapeutics Initiative summarized concerns about the use of dabigatran for atrial fibrillation as follows:

- Licensing of dabigatran 150 mg B.I.D. for atrial fibrillation is premature, pharmacologically irrational, and unsafe for many patients.
- The optimal dose of dabigatran for nonvalvular atrial fibrillation is not yet clear.
- An independent audit of RE-LY is needed to check for irregularities in conduct, sources of bias, and the cause of the unusually high incidence of intracranial hemorrhage in the warfarin arm.
- An independently conducted double-blind RCT comparing dabigatran with warfarin in patients with nonvalvular atrial fibrillation is required.

Table 2. Rate of hemorrhagic stroke in Sportif V, a North American RCT of warfarin, versus rates in warfarin arms of multinational RCTs.

Trial	Drug	Sample size (n/N)	Number of countries	Trial duration (years)	TTR (%)	HS rate (%)
Sportif V	warfarin	2/1962	2	1.7	68	0.1
Sportif III	warfarin	9/1703	22	1.5	66	0.4
RE-LY	warfarin	45/6022	44	2.0	64	0.7
Rocket-AF	warfarin	50/7082	45	2.0	55	0.7
Aristotle	warfarin	78/9081	39	1.8	62	0.8
ENGAGE	warfarin	90/7036	46	2.8	68	0.9

TTR = time in therapeutic range
HS = hemorrhagic stroke

- Taking antiplatelet drugs in combination with oral anticoagulants doubles the incidence of major bleeding events.

It is time to recognize that the conclusions reached by the Therapeutics Initiative require our serious attention, not only with respect to dabigatran, but also with respect to other NOACs. The ball is now in the court of Health Canada, the Canadian Cardiovascular Society, and the Canadian Agency for Drugs and Technologies in Health. It is time to properly address these issues. The status quo is unacceptable.

The RE-LY authors reported that dabigatran 150 mg had double the GI hemorrhage rate of warfarin at a TTR greater than 72.6%.

Competing interests

Dr Trusler is vice-president of INR Online Canada Limited, a nonprofit enterprise dedicated to the improvement of anticoagulation management in Canada. Dr Trusler has not received any financial remuneration from any source, including INR Online Canada Limited or INR Online. INR Online is a not-for-profit company holding the licence for INR Online software in Canada. Once revenues are generated, all funds in excess of operating expenses will be donated to the Warfarin Information Network, a Canadian charitable organization dedicated to the improvement of warfarin management in Canada through education and research.

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