An international perspective on the use of dabigatran

Dear Editor,

One of the promoted advantages of dabigatran over warfarin, on the basis of the RE-LY trial, was the unexpectedly high intracranial haemorrhage rate in the control (warfarin) arm of the trial. However, a Canadian study involving "real world" data from 125 195 patients in Ontario, the intracranial haemorrhage rate over a mean period of five years, was calculated at 0.2% per person year.[1] This compares to dabigatran 150 mg bid at 0.3% per person year in RE-LY.

The INR percentage time in therapeutic range (TTR) is unknown in this study, but presumably was in the mid fifties. What would these results look like in an environment where TTRs are in the range of 75% or greater, such as was achieved in the University of Auckland's Community Pharmacist-led Anticoagulation Management Service study? Also, there is latitude to improve warfarin management through the use of computer decision support software and INR point of care testing. With dabigatran, there is no such potential.

Finally, as the time within therapeutic range affects the hemorrhagic stroke rate, the stroke and systemic embolism rate, the total bleeding rate and the mortality rate, perhaps the RE-LY data should be adjusted to properly place it in context with the real world in Canada, as the valid transferability of the RE-LY (Rocket-AF and Aristotle) findings to Canada (and perhaps New Zealand) is highly in question in our minds.

***Dr Murray Trusler**, MD, MBA, FCFP*
BC, Canada

1. Gomes T, Mamdani M, Holbrook A, et al. Rates of hemorrhage during warfarin therapy for atrial fibrillation. CMAJ 2013;185(2)E121-7.

Thank you for your comments regarding recent BPJ articles on the role of dabigatran in the reduction of thromboembolism in patients with atrial fibrillation (BPJ 50, Feb 2013 and BPJ 38, Sept 2011). We believe the RE-LY multi-centre study provides valuable information for improving patient focused decision making for therapeutic options for patient with atrial fibrillation in New Zealand.

Your comments raise a number of questions:

Are the rates of intracranial haemorrhage over-represented in the New Oral Anti-Coagulant Trials (RE-LY, Rocket-AF and Aristotle)?

The intracranial haemorrhage rate is influenced by the characteristics of the group studied. Cohorts with a higher prevalence of hypertension, previous TIA/stroke and those with higher average $CHADS_2$ scores will be at increased risk of intracranial haemorrhage.[1] The concurrent use of aspirin was the most important modifiable independent risk factor for intracranial haemorrhage in RE-LY.[2]

The Canadian review looked at a real-world population initiated on warfarin for atrial fibrillation, and followed up for five years. The intracranial haemorrhage rate in this study was 0.4% per person year in the first 30 days and 0.2% over the subsequent five years.[3] The two year RE-LY study had an intracranial haemorrhage rate of 0.23% for dabigatran 110 mg, twice daily, 0.32% for 150 mg, twice daily and 0.76% for the matched warfarin arm.[4] Individuals enrolled in the RE-LY and Canadian studies had similar risk factors for intracranial haemorrhage (mean $CHADS_2$ scores of approximately 2 and similar rates of previous stroke and hypertension). However, participants in the RE-LY study had nearly twice the rate of aspirin use which may account in part for the higher intracranial haemorrhage rate.

The Rocket- AF trial had a cohort that were much more "at risk" for intracranial haemorrhage. Past history of TIA and stroke was 52% compared to 21.3% in the Canadian study, mean $CHADS_2$ score was 3.48 as opposed to just over 2 and an aspirin use was 29% as opposed to 20% in the Canadian study. The intracranial haemorrhage rate for the warfarin arm in Rocket was 0.7%. The higher rate of intracranial haemorrhage can be, in part, explained by the different cohort characteristics.[5]

What are the benefits of dabigatran over well-managed warfarin, as represented by time in therapeutic range (TTR)?

For patients taking warfarin, the TTR also has an effect on intracranial haemorrhage rates.[3] In RE-LY the INR control was relatively poor (TTR – 64%).[6] TTR was not evaluated in the Canadian AF warfarin study.

To analyse the effect of warfarin control on the end points of the study, RE-LY looked at two measures: the individual time in therapeutic range (iTTR) and the mean time in therapeutic range for each study centre (cTTR).[6]

The table below illustrates the reduction in end point events with improving TTR for individual patients taking warfarin in RE-LY. The greater the time in the therapeutic range, the better the outcomes.

	AF Warfarin patients – Percentage Time in Therapeutic Range (iTTR) Divided up in quartiles i.e. 25% of patients fell into following groups[6]			
Events:	**< 53.6 %**	**53.6 – 67.2 %**	**67.2 – 78.4 %**	**> 78.4 %**
Stroke and systemic embolic episodes	2.34%	1.72%	1.42%	1.25%
Major bleeding	4.95%	3.71%	2.98%	2.65%
Total mortality	7.48%	3.30%,	2.27%	2.65%
Composite	12.32%	7.35%	5.55%	5.4%

Irrespective of the centres quality of warfarin management (cTTR) the rate of intracranial bleeds was lower for both doses of dabigatran than with warfarin, and this did not change even for centres that had a cTTR of > 72.6%. However, dabigatran 150 mg was not superior to warfarin in reducing the risk of non-haemorrhagic stroke when the cTTR was > 72.6%. Also, there were no advantages for dabigatran over warfarin for outcomes such as non-haemorrhagic events and mortality, when cTTR for warfarin was >72.6%.[6]

These results show the importance of clinicians understanding the mean cTTR for all patients in their practice taking warfarin, and calculating individual iTTRs when considering changing patients from warfarin to dabigatran.

What are the implications for clinicians making decisions on treatment options for individual patients?

From "The use of dabigatran in general practice", BPJ 38 (Sep, 2011):

Patients with non-valvular atrial fibrillation **who may benefit** from dabigatran include those who:

- Require anticoagulation but are currently on no treatment, e.g. patients who have declined treatment with warfarin or aspirin or those taking medicines that are contraindicated with warfarin
- Are already on warfarin but where there are difficulties with monitoring, e.g. difficult venous access, problems with accessing lab facilities due to mobility issues, cost or lack of time, those who are non-compliant with monitoring
- Are already on warfarin but have INR values that are often sub-therapeutic or difficult to control
- Wish to change for convenience

Patients who **may not benefit** from dabigatran include those who:

- Are on warfarin with a stable (or easy to control) INR and who are comfortable with the need for INR monitoring.
- Patients on warfarin who have INR values that are consistently within the therapeutic range are less likely to benefit from a switch to dabigatran.
- Are unlikely to be compliant with the twice daily dosing required for dabigatran
- Prefer to continue with warfarin (some patients may like the reassurance of periodic monitoring)
- Require blister packed medicines

Decision support tools for warfarin management

We agree with the correspondent that every effort should be made to improve TTR when warfarin is the preferred therapeutic option for preventing thromboembolism in atrial fibrillation. Decision support has an important role in:

1. Deciding to initiate oral anticoagulants over aspirin/ clopidogrel in atrial fibrillation.
2. Deciding when TTR for warfarin is insufficient to be comparable to dabigatran.
3. Advising on warfarin dose and review periods to maintain cTTR above 72.6% at practices.

References:

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6. Wallentin L, Yusef S, Ezekowitz M, et al. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. Lancet 2010;376(9745):975–83.

Escitalopram also associated with QT interval prolongation

Dear Editor,

The risk of QT interval prolongation with citalopram has been well described in your article "Prescribing citalopram safely: an update", BPJ 42 (Feb, 2012). However, your suggestion to switch to "a lower risk SSRI such as escitalopram might be more appropriate" may not be true. Escitalopram overdose leading to prolongation of the QTc interval has been previously described in the literature. The recommendation suggested in this update may be misleading to the prescribers.

Dr Prasad Nishtala, *Clinical Pharmacist*
Dunedin

When safety warnings first emerged in regards to the risk of QT prolongation with high-dose citalopram, it was advised that the recommended maximum daily dose be lowered to 40 mg. As escitalopram already had a recommended maximum daily dose of 10 – 20 mg, which is equivalent to the lowered maximum dose of citalopram, the same warnings were not issued for escitalopram.[1]

Prescribers were advised to review patients taking high doses of citalopram, and reduce their daily dose to ≤ 40 mg. A suggested alternative was to switch to a standard dose of escitalopram, which is considered safer in terms of cardiac toxicity, than a high dose of citalopram. However, the correspondent is correct in that escitalopram is not "a lower risk SSRI".

After evaluating case and trial data, the United States Food and Drug Administration (FDA) found that QT interval prolongation increased, with increasing doses of citalopram; there was a mean prolongation of 8.5 ms with 20 mg/day, 12.6 ms with 40 mg/day and 18.5 ms with 60 mg/day. The QT interval was also prolonged with increasing doses of escitalopram, but to a lesser extent; there was a mean prolongation of 4.5 ms with 10 mg/day, 6.6 ms with 20 mg/day and 10.7 ms with 30 mg/day.[2] Therefore the recommended daily dose of escitalopram (10 – 20 mg) is associated with a lower clinical risk of cardiac adverse effects than an equivalent dose of citalopram (40 mg), but still has a higher risk than some other antidepressant medicines.

Fluoxetine, paroxetine and sertraline are considered unlikely to cause prolonged QT interval when used at recommended doses in people without risk factors. Prospective studies have not found any evidence of QT prolongation with these medicines, however, case reports (some of limited validity) exist linking all SSRIs, except paroxetine, to QT interval prolongation and/or Torsades De Pointes.[3] All tricyclic antidepressants can cause QT interval prolongation.[3]

In summary, patients with risk factors for QT prolongation, taking other medicines that can cause QT prolongation or with severely reduced renal function, may be cautiously prescribed citalopram or escitalopram, provided that QT interval is monitored at baseline and intermittently throughout treatment, and that doses do not exceed maximum daily recommendations (≤ 40 mg for citalopram and ≤ 20 mg for escitalopram). Sertraline may be a more appropriate antidepressant for people at increased cardiac risk, as it has few medicine interactions, has not been consistently linked to QT prolongation, and is the most studied antidepressant medicine in patients with cardiac abnormalities.[3]

To switch to sertraline, the patient can stop citalopram or escitalopram, then start sertraline the next day. Sertraline is started at 50 mg daily, tapered upward, in steps of 50 mg at intervals of at least one week to a maximum of 200 mg daily, until a positive clinical benefit is observed. The usual maintenance dose for most people is 50 mg daily.[4]

References

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Write to us at: Correspondence, PO Box 6032, Dunedin or email: editor@bpac.org.nz