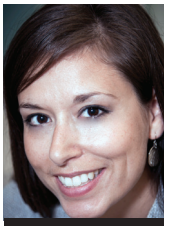
Dabigatran in atrial fibrillation: New kid on the block

Timothy S. Leung, BScPharm; Miriam Fradette, BScPharm, ACPR; Ann Thompson, BScPharm, PharmD, ACPR; Sheri L. Koshman, BScPharm, PharmD, ACPR

T. Leung



S. Koshman

While the novel anticoagulant dabigatran offers benefits over existing therapies, its limited "real world" experience should guide its use cautiously in select patient populations. Given the increased uptake of this agent, our aim was to provide readers with a practical overview of dabigatran, highlighting its safety, efficacy and some of its emerging issues and controversies.

Bien que le nouvel anticoagulant dabigatran offre des avantages par rapport aux traitements existants, son utilisation auprès des populations de patients choisies devrait se faire avec prudence, étant donné l'expérience limitée de son administration en « situations réelles ». Eu égard à la popularité croissante de ce médicament, notre objectif était de présenter aux lecteurs une vue d'ensemble pratique du dabigatran, notamment de son innocuité, de son efficacité et de certaines questions et controverses nouvelles y afférentes.

In Canada, atrial fibrillation (AF) is the most prevalent cardiac arrhythmia.[1] It is associated with an increase in morbidity and mortality, with cardioembolic stroke being one of the most feared complications.[2] Anticoagulation is an effective means of reducing the risk of stroke. Currently, warfarin is the preferred agent in patients at high risk of stroke.[3,4] However, maintaining warfarin therapy within its narrow therapeutic window is challenging, even for specialized anticoagulation clinics.[5] Many factors contribute to the variable dose response of warfarin, such as inter-individual variability, comorbidities and drug and food interactions.[5] Dabigatran is a novel therapeutic alternative that provides more predictable anticoagulation with less laboratory monitoring, and it is poised to take over some of warfarin's role in AF stroke prophylaxis. While other novel agents, such as rivaroxaban and apixaban, have proven to be beneficial in stroke prophylaxis in AF, discussion of their roles is beyond the scope of this article.

Dabigatran etexilate is a reversible, direct thrombin inhibitor administered orally as a prodrug. By inhibiting thrombin, the final step of the clotting cascade, it prevents stabilization of thrombus formation by impairing fibrinogen conversion to fibrin.[6] Direct inhibition of this final step of coagulation results in anticoagulation within hours, as plasma concentration of dabigatran and degree of anticoagulant effect are directly proportional to each other.[7] In contrast, warfarin's anticoagulation is due to its indirect effects on the clotting cascade, taking several days to inhibit hepatic synthesis of vitamin K–dependent clotting factors.[5] Its full anticoagulant effects are not realized until circulating clotting factors are eliminated.

Dabigatran etexilate has poor bioavailability and requires an acidic environment for absorption. To increase bioavailability and gastric acidity, it has been specially formulated with a tartaric acid core.[7] Because of this formulation, the capsule needs to be swallowed whole and kept in its original packaging to maintain product stability. Food does not affect bioavailability, but will increase time required to reach peak plasma levels. Once absorbed, the prodrug is rapidly converted to the active form by esterases and moderately distributed into tissues.[7] It is not metabolized by the cytochrome P450 enzymes and is primarily renally excreted (>85%).[7] Because a large proportion of the drug is renally eliminated, plasma drug concentrations will increase in patients with impaired renal function, thereby increasing the risk for adverse events, namely bleeding. Dabigatran is contraindicated in severe renal dysfunction (CrCl <30 mL/min).[7] A half-life of 12–17 hours can be expected with dabigatran, necessitating twice-daily dosing.[8] Steady state is expected within 3 days in patients with normal renal function.[9]

Another advantage of dabigatran over warfarin is fewer drug interactions. Dabigatran, however, is not without interactions. It is a substrate of P-glycoprotein (P-gp), whose anticoagulant effects are expected to increase with concomitant use of P-gp inhibitors and decrease with concurrent use of P-gp inducers.[7] Additionally, concomitant use

of acid-suppressing therapies such as antacids can affect absorption; therefore, it is recommended that dabigatran be administered ≥2 hours prior to antacid use.[7] Histamine-2 receptor antagonists and proton pump inhibitors may also reduce clinical effectiveness; however, no dose adjustment is recommended in the product monograph.[7] Table 1 summarizes noteworthy drug interactions.

Clinical data

There is only a single landmark trial that has evaluated dabigatran in AF. The RE-LY trial (**R**andomized **E**valuation of **L**ong-term anticoagulation therap**Y**)[10] randomized 18,113 individuals to receive dabigatran 110 mg twice daily, dabigatran 150 mg twice daily or warfarin (INR 2-3). The trial was designed to show noninferiority of dabigatran compared to warfarin for the prevention of stroke and systemic emboli. Approximately 64% of patients were men, with a mean age of 71 (±8.6) years. The mean $CHADS_2$ score was 2.1±1.2, with approximately 67% of the population having a score ≥2. Approximately 20% of patients previously had a stroke or a transient ischemic attack. The sample was evenly split in terms of type of atrial fibrillation (e.g., persistant, paroxysmal and permanent). Fifty percent of patients had been on warfarin prior to randomization. Both dabigatran arms were blinded; however, the warfarin arm was open label. Inclusion and exclusion criteria are listed in Table 2. Median follow-up time was 2 years. At baseline, 40% of patients were taking ASA and approximately 20% of people in each arm continued ASA use throughout the study. Patients on warfarin had a therapeutic INR for 64% of the study period, which is similar to other reported warfarin clinical trials.[11,12]

The RE-LY trial demonstrated that dabigatran 110 mg twice daily was noninferior to warfarin (relative risk [RR] 0.91 [95% confidence interval (CI) 0.74–1.11, $p < 0.001$]), while dabigatran 150 mg twice daily was superior to warfarin (RR 0.66 [95% CI 0.53–0.82, $p < 0.001$]) for reducing stroke and systemic embolism in patients with AF.[10] There were also significantly lower rates of hemorrhagic stroke in both dabigatran groups (110 mg RR 0.31[95% CI 0.17–0.56, $p < 0.001$]; 150 mg RR 0.26 [95% CI 0.14–0.49, $p < 0.001$]). In patients taking dabigatran 150 mg twice daily, a trend of increased risk of myocardial infarction

TABLE 1 Drug-drug interactions with dabigatran[7*]

Effect on dabigatran concentration	Drug	Details
Increase	Amiodarone	Exposure increase of 60% (no dose adjustment recommended, caution, increase monitoring)
	Ketoconazole	Exposure increase of 150% (contraindicated)
	Quinidine	Exposure increase of 53% (no dosage adjustment recommended, minimize interaction by giving dabigatran 2 hours prior)
	Verapamil	Magnitude dependent on timing and formulation used (no dosage adjustment recommended, minimize interaction by giving dabigatran 2 hours prior)
Decrease	St. John's wort	Co-administration not recommended
	Carbamazepine	Co-administration not recommended
	Rifampin	Exposure decrease by 67% (co-administration should be avoided)

*Note that these are interactions identified in the product monograph and do not include all P-gp inhibitors/inducers.

TABLE 2 Inclusion and exclusion criteria for the RE-LY Trial[10]

Inclusion	Exclusion
Patients with AF and at least one of the following: • Previous stroke/transient ischemic attack • Left ventricular ejection fraction <40% • NYHA class II-IV heart failure in the 6 months prior • ≥ 75 years old **OR** • 65–74 years old with one of: type 2 diabetes mellitus, hypertension or coronary artery disease.	• Severe valvular heart disease • Stroke within 14 days or severe stroke within 6 months • CrCl <30 mL/min • Active liver disease • Pregnancy • Conditions that increase risk of hemorrhage

NYHA: New York Heart Association.

(MI) was observed. Re-evaluation and analysis of study data, as requested by the FDA, showed that the increase in risk of MI is not statistically significant (RR 1.27 [95% CI 0.94–1.71, $p = 0.12$]), however, controversy around this topic still exists.[13] Recently, more data have been published regarding the details of MI and myocardial ischemic events.[14] This data demonstrated that there was no difference in myocardial ischemic events between treatment groups and there was no difference in event rates in those patients with a previous history of myocardial ischemic events. Furthermore, an on-treatment analysis revealed that 30% of subjects were off study drug at the time of their events. The authors also postulated that because warfarin has been proven to decrease MI, perhaps the increase in MI is merely a lack of effect of dabigatran on the outcome of MI when compared to warfarin rather than a true increase in events. Details on the RE-LY results are listed in Table 3.

Rates of bleeding for each group are outlined in Table 4. Dabigatran 110 mg twice daily was associated with a significantly lower risk of major bleeds (RR 0.80 [95% CI 0.70–0.93, $p = 0.003$]), while those patients receiving dabigatran 150 mg twice daily had similar rates of major bleeds to warfarin (RR 0.93 [95% CI 0.81–1.07, $p = 0.32$]). Rates of intracranial bleeds were significantly reduced with both doses of dabigatran compared to warfarin (110 mg RR 0.31[95% CI 0.20–0.47, $p < 0.001$]; 150 mg RR 0.40 [95% CI 0.27–0.60, $p < 0.001$]). A significant increase in rate of gastrointestinal bleeds was observed in patients taking the higher dose of dabigatran (RR 1.50 [95% CI 1.19–1.89, $p < 0.001$]) compared to warfarin.

It should be noted that rates of discontinuation were higher after 2 years of follow-up for dabigatran (21% for both doses compared to 17% for warfarin, $p < 0.001$).[10] Dabigatran was also associated with higher rates of dyspepsia. This is perhaps due to the capsule's tartaric acid core. There did not appear to be a difference between doses.

Canadian Cardiovascular Society AF Guidelines

The results of RE-LY are reflected in the 2010 Canadian Cardiovascular Society Atrial Fibrillation Guidelines.[15] The guidelines recommend

TABLE 3 Efficacy endpoints for RE-LY Trial[10,13]

Efficacy outcomes *n* (%/yr)	Warfarin (*n* = 6022)	Dabigatran		Number needed to treat per year	
		110 mg bid (*n* = 6015)	150 mg bid (*n* = 6076)	110 mg	150 mg
Primary outcome: Stroke or systemic embolism	202 (1.71)	183 (1.54)	134 (1.11)	NS noninferior	166
All stroke	185 (1.57)	171 (1.44)	122 (1.01)	NS	178
Ischemic stroke	142 (1.20)	159 (1.34)	111 (0.92)	NS	357
Hemorrhagic stroke	45 (0.38)	14 (0.12)	12 (0.10)	384	357
Myocardial infarction	75 (0.64)	98 (0.82)	97 (0.81)	NS	NS
All-cause mortality	487 (4.13)	446 (3.75)	438 (3.64)	NS	NS

NS = not statistically significant; $p > 0.05$; bid = twice daily.

TABLE 4 Safety endpoints for RE-LY Trial[10,13]

Safety endpoints *n* (%/yr)	Warfarin (*n* = 6022)	Dabigatran		Number need to harm per year	
		110 mg bid (*n* = 6015)	150 mg bid (*n* = 6076)	110 mg bid	150 mg bid
Major bleed*	421 (3.57)	342 (2.87)	399 (3.32)	–143	NS
Gastrointestinal bleed	120 (1.02)	133 (1.12)	182 (1.51)	NS	204
Intracranial bleed†	87 (0.74)	27 (0.23)	36 (0.30)	–196	–227
Minor bleed‡	1931 (16.37)	1566 (13.16)	1787 (14.84)	–31	–65
Net clinical benefit§	901 (7.64)	844 (7.09)	832 (6.91)	NS	–136

NS = not statistically significant; bid = twice daily; $p > 0.05$.

*Major bleed defined as: ↓ Hgb ≥20 g/L, transfusion of ≥2 units of blood, symptomatic bleeding in critical area or organ, life-threatening bleeding (fatal bleeding, symptomatic intracranial bleeding, bleeding with decrease in Hgb ≥50 g/L, transfusion of ≥4 units of blood).

† Intracranial hemorrhage consisted of hemorrhagic stroke and subdural or subarachnoid hemorrhage.

‡ Minor bleed defined as bleeding not classified as major bleeding.

§ Net clinical benefit defined as a composite of the primary endpoint, PE, MI and major hemorrhage.

KEY POINTS

- Dabigatran was the first novel anticoagulant to be approved in Canada for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.
- In comparison to warfarin, dabigatran (150 mg twice daily) is more effective in reducing the incidence of stroke and systemic embolism, while rates of major bleeding are similar. Dabigatran (110 mg twice daily) is associated with lower bleeding rates, but similar rates of stroke and systemic embolism. The lower dosage should be considered for patients >80 years, or >75 years with risk factors for bleeding or reduced renal function.
- Dabigatran overcomes many of the limitations associated with warfarin, including more predictable anticoagulant effects, no lab monitoring (INR) and subsequent dosage adjustments, fewer drug-drug interactions and no known drug-food interactions. There is, however, no reversal agent for dabigatran at the present time and cases of fatal bleeding have been reported.
- Longer-term efficacy and safety data are lacking.

use of warfarin (INR 2-3) or dabigatran for AF patients with a $CHADS_2$ score ≥ 1, unless the risks of therapy (i.e., bleeding) outweigh the benefits or there is contraindication to the therapy. The guidelines recommend that for most patients, dabigatran is preferred over warfarin. Notable exceptions are those with a propensity to dyspepsia, gastrointestinal bleeding or those with a substantial risk of coronary events, including those with stable coronary disease. Preference is also given to the 150 mg twice-daily dose, except in patients with low body weight (not specified), decreased renal function (not specified) or an increase risk of major bleeding.

It is important to note that these recommendations place greater weight on absolute stroke risk reduction than absolute increase risk of hemorrhage. In addition, more weight is placed on the aforementioned advantages of dabigatran than the long safety experience with warfarin.

Place in therapy

Given its clinical data and recommendation in the newly updated atrial fibrillation guidelines, dabigatran has become a very attractive option in the prevention of stroke in nonvalvular AF. The much debated question is whether it will overtake warfarin as the preferred therapeutic agent in moderate-high-risk patients. A few points warrant discussion and relate to the uptake of this new therapeutic modality in Canada. First, one must keep in mind that there has only been a single outcome trial, albeit large and well designed, published on the use of dabigatran for stroke prophylaxis.[10] This trial was done in a select population and may not be generalizable to all patients with AF. Specifically, those with a recent stroke, valvular AF (including mechanical heart valves) and those with renal dysfunction (CrCl <30 mL/min) or hepatic dysfunction were not studied.

Additionally, unlike warfarin, there is no antidote to reverse the anticoagulation effects of dabigatran. This will need to be taken into serious consideration when deciding to use this agent in a patient at high risk of bleeding. Indeed, postmarket surveillance is identifying issues with bleeding, including fatal cases of bleeding. Safety advisories have been issued in Japan, Australia and the UK, and the US Food and Drug Administration is investigating serious bleeding events.[16] There have also been monograph updates in both Europe and the US advocating for increased monitoring of renal function.[17] The Institute for Safe Medication Practices recently reported an increase in bleeding reports related to dabigatran. A quarter of these reports were in elderly patients, raising the concern of safety in this patient population, perhaps related to decreasing renal function.[18] Lastly, given that this is a new agent, there is no long-term safety data compared to warfarin. An extension of the RE-LY study, RELY-ABLE, is currently underway to evaluate safety up to 28 months.[19]

One of the most important determinants of uptake will likely be cost and whether or not it will be covered by provincial payers. The Common Drug Review (CDR) recommended that dabigatran be listed as a drug benefit only in patients who have had a hypersensitivity reaction to warfarin or in those patients for whom warfarin is indicated, but who fail to achieve adequate INR control despite close monitoring and dosage adjustments.[20] Furthermore, they also recommend that these patients should be referred to an anticoagulation management service if available, in an attempt to maintain better control. The rationale behind this recommendation references the RE-LY trial and a pre-defined subgroup analysis, showing that in those centres that had good INR control (in the therapeutic range >65.5% of the time), dabigatran 150 mg twice daily was no longer superior to warfarin for the primary outcome of stroke and systemic embolism. Cost was also cited as a deciding factor ($3.20/day for dabigatran and $1.16/day for warfarin + monitoring costs). While these 2 reasons were listed as the primary rationale for the recommendation, the CDR also listed other considerations, including a low absolute risk reduction compared to warfarin, the contraindication

POINTS CLÉS

- Le dabigatran était le premier anticoagulant nouveau, qui a été approuvé au Canada pour la prévention de l'accident vasculaire cérébral et de l'embolie systémique chez les patients atteints de fibrillation auriculaire non valvulaire.
- Le dabigatran (150 mg, deux fois par jour) est plus efficace que la warfarine pour réduire l'incidence d'accident vasculaire cérébral et d'embolie systémique; les taux d'hémorragies majeures associées à ces deux médicaments sont toutefois comparables. À une dose plus faible (110 mg, deux fois par jour), le dabigatran est associé à des taux de saignement moindres, mais les taux d'accident vasculaire cérébral et d'embolie systémique sont comparables. La plus faible posologie devrait être envisagée pour les patients âgés de plus de 80 ans ou ceux de moins 75 ans qui présentent des facteurs de risque de saignement ou une fonction rénale réduite.
- Le dabigatran élimine bon nombre des limites associées à la warfarine, notamment en produisant des effets anticoagulants plus prévisibles, en n'exigeant aucune analyse de suivi (RIN) ni ajustement subséquent de la dose, en causant moins d'interactions médicament-médicament et en n'ayant aucune interaction connue avec les aliments. Cependant, il n'existe à l'heure actuelle aucun médicament qui permette de contrecarrer l'action du dabigatran et certains cas d'hémorragie fatale ont été signalés.
- Enfin, on ne possède aucune donnée sur l'innocuité et l'efficacité de ce médicament à long terme.

in renal dysfunction and impact on the targeted elderly population, and the issue of no reversal agent. Dabigatran currently has limited provincial coverage in Quebec only. Uptake will likely be limited by whether or not other provinces add it to their provincial formularies.

Conclusion

Dabigatran has been shown to be noninferior (110 mg bid) and superior (150 mg bid) to warfarin in reducing the risk of thromboembolic complications in patients with nonvalvular AF, with similar hemorrhagic rates. Management of this medication is less complicated than warfarin, given its more predictable anticoagulant effects, lack of routine lab monitoring and fewer drug interactions. These benefits need to be weighed against potential downfalls, such as the specific population it has been studied in, lack of reversibility, bleeding complications and its acquisition costs. However, overall, dabigatran is an attractive and welcome addition to the options for stroke prophylaxis in AF. Stay tuned for more data on direct thrombin inhibitors coming soon. ■

From the Faculty of Pharmacy and Pharmaceutical Sciences (Leung, Thompson) and the Faculty of Medicine and Dentistry (Fradette, Koshman), University of Alberta, Edmonton, Alberta. Contact sheri.koshman@ualberta.ca.

References

1. Foerster V. New anticoagulants for stroke prevention in patients with atrial fibrillation. Issues in emerging health technologies 2010; issue 116. Available: http://cadth.ca/media/pdf/R0004_Anticoagulants_Atrial_Fibrillation_cetap_e.pdf (accessed January 26, 2011).

2. Holmes DR Jr. Atrial fibrillation and stroke management: present and future. *Semin Neurol* 2010;30:528-36.

3. Marsh JD, Keyrouz SG. Stroke prevention and treatment. *J Am Coll Cardiol* 2010;56:683-91.

4. Ezekowitz MD, Aiken TH, Brown A, Ellis Z. The evolving field of stroke prevention in patients with atrial fibrillation. *Stroke* 2010;41[suppl 1]:S17-S20.

5. Bungard TJ, Gardner L, Archer SL, et al. Evaluation of a pharmacist-managed anticoagulation clinic: improving patient care. *Open Med* 2009;3(1):16-21.

6. Fogarty PF, Minichiello T. Chapter 14: Disorders of hemostasis, thrombosis & antithrombotic therapy. In: McPhee SJ, Papakakis MA, Rabow MW, Cucina R. Current Medical Diagnosis & Treatment 2011. *McGraw-Hill Companies, Inc.*; 2011.

7. Pradax product monograph. e-CPS. Available: www.e-therapeutics.ca (accessed January 20, 2012).

8. Eisert WG, Hauel N, Stangier J, et al. Dabigatran: a novel potent reversible nonpeptide inhibitor of thrombin. *Arterioscler Thromb Vasc Biol* 2010;30:1885-9.

9. Siddiqui FM, Qureshi AI. Dabigatran etexilate, a new oral direct thrombin inhibitor, for stroke prevention in patients with atrial fibrillation. *Expert Opin Pharmacother* 2010;11(8):1403-11.

10. Connolly SJ, Ezekowitz MD, Yusuf S, et al., and the RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361:1139-51.

11. Wallentin L, Yusuf S, Ezekowitz MD, et al. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalized ratio control from stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. *Lancet* 2010;376:975-85.

12. Dolan G, Smith LA, Collins S, Plumb JM. Effect of setting, monitoring intensity and patient experience on anticoagulation control: a systematic review and meta-analysis of the literature. *Curr Med Res Opin* 2008;24(5):1459-72.

13. Connolly SJ, Ezekowitz MD, Yusuf S, et al., for the Randomized Evaluation of Long-Term Anticoagulation Therapy Investigators. Newly identified events in the RE-LY Trial. *N Engl J Med* 2010;363:1875-6.

14. Hohnloser SH, Oldgren J, Yang S, et al. Myocardial ischemic events in patients with atrial fibrillation treated with dabigatran or warfarin in the RE-LY trial. *Circulation* 2012;125:669-76.

15. Cairns JA, Connolly S, McMurtry S, et al., and the CCS Atrial Fibrillation Guidelines Committee. Canadian Cardiovascular Society Atrial Fibrillation Guidelines 2010: prevention of stroke and systemic thromboembolism in atrial fibrillation and flutter. *Can J Cardiol* 2011;27:74-90.

16. U.S. Food and Drug Administration. FDA Drug Safety Podcast for Healthcare Professionals: safety review of post-market reports of serious bleeding events with the anticoagulant Pradaxa (dabigatran etexilate mesylate). Available: www.fda.gov/Drugs/DrugSafety/DrugSafetyPodcasts/ucm283151.htm (accessed January 20, 2012).

17. O'Riordan M. FDA investigating serious bleeding events with dabigatran. Available: www.medscape.com/viewarticle/754953 (accessed January 20, 2012).

18. Institute for Safe Medication Practices. ISMP Medication Safety Alert. Quarterwatch (first quarter 2011) signals for dabigatran and metoclopramide. Available: www.ismp.org/Newsletters/acutecare/showarticle.asp?ID=12 (accessed January 20, 2012).

19. RELY-ABLE Long Term Multi-center Extension of Dabigatran Treatment in Patients with Atrial Fibrillation who Completed RE-LY Trial. Available: http://clinicaltrials.gov/ct2/show/NCT00808067 (accessed June 6, 2011).

20. Canadian Agency for Drugs and Technologies in Health. Common Drug Review. CEDAC Final Recommendation. Dabigatran etexilate. New indication: prevention of stroke and systemic embolism in patients with atrial fibrillation. Available: www.cadth.ca/media/cdr/.../cdr_complete_Pradax_June-27-11.pdf/ (accessed January 20, 2012).