Dabigatran in atrial fibrillation

Dabigatran etexilate (Pradax™), a direct thrombin inhibitor, is an oral anticoagulant marketed for the prevention of stroke and systematic embolism in at-risk patients with non-valvular atrial fibrillation (AF).

Dabigatran should not be prescribed for patients with prosthetic heart valves or other significant valvular heart diseases due to lack of evidence for efficacy and safety in this patient population. There is currently no known specific antidote to treat dabigatran-induced bleeding.

Warfarin has been used for over 60 years and is safe and effective especially when supported with a structured care plan (e.g., education, INR testing and interpretation, dose adjustments, and side effect monitoring). The Canadian Agency for Drugs and Technologies in Health (CADTH) has recently published reports and practice tools to support optimal warfarin use (http://cadth.ca/en/products/optimal-use/warfarin-management). When a structured approach is used, **most patients can be adequately managed on warfarin therapy**. Until longer-term data becomes available and an effective antidote has been identified for these newer anticoagulants, warfarin still appears to be the safest and most cost-effective agent for most patients.

RE-LY: Dabigatran's pivotal clinical trial

RE-LY (Randomized Evaluation of Long-term Anticoagulation Therapy) is the only published randomized controlled trial that evaluated the efficacy and safety of dabigatran for prevention of stroke and systemic embolism in patients with **non-valvular** AF and other risk factors.[1,2] In this trial, 18,113 patients were randomized to receive dabigatran 110 mg or 150 mg twice daily (blinded) or open-label, adjusted-dose warfarin. Median follow-up time was 24 months.[1]

Efficacy—For the primary composite efficacy endpoint (stroke and systemic embolism), dabigatran 110 mg was found to be non-inferior to warfarin (Relative Risk, or RR = 0.90; 95%CI: 0.74-1.10),[2] while dabigatran 150 mg was superior to warfarin (RR 0.65; 95%CI 0.52-0.81).[2] However, in a pre-planned subgroup analysis,[3] the superiority of dabigatran 150 mg was limited only to patients with poor INR control (i.e., time in therapeutic range < 65%).

Currently, there is no validated clinical test to monitor dabigatran's efficacy.

Safety—During the short duration (2-year) of the RE-LY trial, dabigatran 110 mg was associated with lower rates of major bleeding and intracranial bleeding compared to warfarin. However, dabigatran 150 mg was associated with a **higher rate of GI bleeding, dyspepsia, and therapy discontinuation in the trial**.[1,2] There was also a trend to increased myocardial infarction in the dabigatran-treated groups.[1,2]

Safety Outcomes	Dabigatran	
	110 mg BID	150 mg BID
Major bleeding	RR 0.80* (vs. warfarin; 95%CI: 0.70-0.93) ARR 0.70%/yr	NSS (vs. warfarin)
Intracranial bleeding	RR 0.30* (vs. warfarin; 95%CI: 0.19-0.45) ARR 0.53%/yr	RR 0.41*(vs. warfarin; 95%CI 0.28-0.60) ARR 0.44%/yr
Gastro-intestinal bleeding	NSS (vs. warfarin)	RR 1.48*(vs. warfarin; 95%CI 1.18-1.85) ARI 0.49%/yr

Abbreviations: **ARI** absolute risk increase; **ARR** absolute risk reduction; **BID** twice daily; **CI** confidence interval; **INR** international normalized ratio; **mg** milligrams; **NSS** non-statistically significant; **RR** relative risk compared to warfarin

* Denotes statistical significance vs. warfarin

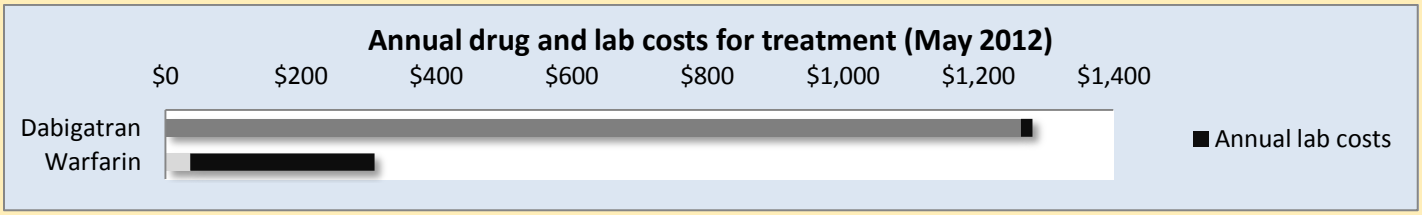
At present there is no established effective antidote for dabigatran.[4] Uncontrolled bleeding may occur and can be difficult to treat. Therefore, **dabigatran should be prescribed only for patients who have ready access to appropriate medical services to manage a major bleeding event**.

Post-marketing information also suggests that dabigatran may be associated with significant risks. Of note, as of December 31, 2011, a total of 476 serious adverse reaction reports were received by Health Canada. Japan, New Zealand, and the United States have issued safety alerts or have expressed concerns about the high number of adverse event reports.

Elderly and patients with renal impairment have increased bleeding risk. Therefore, renal function should be assessed regularly[5] (baseline, at least yearly, and when clinically appropriate). Dabigatran is contraindicated in patients with severe renal impairment (CrCl or eGFR < 30 mL/min). It should not be prescribed for elderly (≥ 75 years of age) without documented stable renal function.[5]

Dabigatran is known to interact with other medications. Consult the latest product monograph for potential drug interactions.

Costs—Dabigatran is significantly more expensive than warfarin. The figure below depicts the combined annual drug and lab monitoring costs for an average patient in B.C. (e.g., 16 INR tests per year for patients on warfarin or one eGFR per year for patients on dabigatran). Note that monitoring should be tailored to the individual patient and more frequent monitoring may be required.



Other considerations—Dabigatran requires twice daily dosing. Therefore, it should not be prescribed for patients who have difficulty adhering to their medication regimens.

How to switch patients from dabigatran to warfarin—There may be situations in which switching back to warfarin is clinically appropriate. To convert from dabigatran to warfarin, measure CrCl and the following regimen can be used[6]:

CrCl > 50 mL/min:	Start warfarin 3 days before discontinuing dabigatran
CrCl 31-50 mL/min:	Start warfarin 2 days before discontinuing dabigatran
CrCl 15-30 mL/min:	Start warfarin 1 day before discontinuing dabigatran

BC PharmaCare Special Authority coverage criteria—Visit www.health.gov.bc.ca/pharmacare/sa/criteria/restricted/dabigatran.html.

References

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