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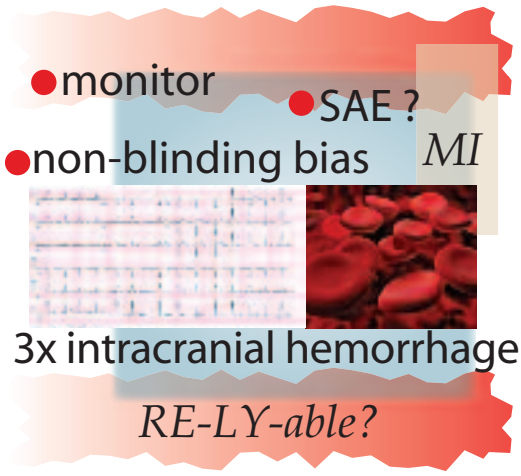
Dabigatran for atrial fibrillation
Why we can not rely on RE-LY



Dabigatran (Pradax®), a direct thrombin inhibitor oral anticoagulant, was licensed in Canada in November 2010 for stroke prevention in patients with non-valvular atrial fibrillation. It is being promoted as an alternative to warfarin with the purported advantage that coagulation monitoring is not required. Do we know enough about dabigatran? It took over 50 years to learn how to use warfarin with reasonable effectiveness and safety for this use.

Health Canada approved dabigatran for this indication largely based on data from the RE-LY trial.[1]

The objective of this Letter is to provide a detailed analysis of the RE-LY trial data from the NEJM paper[1] as well as the more complete data from the US FDA website[2]. Our analysis applies the same hierarchy of health outcomes presented in previous Therapeutics Letters.

The RE-LY trial performed a double-blind comparison between two doses of dabigatran and a non-blinded comparison between dabigatran and warfarin. For the blinded dose comparison, Table 1 shows key health outcomes ranked from most to least severe, using data from both sources.

Table 1: Key outcomes for dabigatran 110 vs 150 mg BID

Outcome	Dabigatran 110mg BID	Dabigatran 150mg BID	RR [95% CI]	ARR ARI
Patients randomized	6015	6076		
Deaths	446	444	1.01	
(FDA)	7.4%	7.3%	[0.89, 1.15]	
Serious adverse events	Not reported	Not reported	?	?
Hospitalizations	2311	2430	0.96	
(NEJM)	38.4%	40%	[0.92, 1.00]	
Disabling and fatal stroke	89	61	1.47	0.5%
(FDA)	1.5%	1%	[1.07, 2.04]	
Intracranial hemorrhage	27	38	0.72	
(FDA)	0.4%	0.6%	[0.44, 1.17]	
MI	86	89	0.98	
(NEJM)	1.4%	1.5%	[0.73, 1.31]	
Bleeds leading to hospitalization minus intracranial hemorrhage (FDA)	259	330	0.79	1.1%
	4.3%	5.4%	[0.68, 0.93]	

Dabigatran 150 mg BID reduced fatal and disabling strokes by 0.5% compared with 110 mg BID and reduced all ischemic strokes by 0.8% (not shown). However, dabigatran 150 mg BID was also more harmful, causing a 1.1% absolute increase in bleeding leading to hospitalization. Total hospitalizations provides an estimate of net health benefit; the numerical difference (1.6%) favouring the lower dose barely misses statistical significance. Based on its benefit for stroke, both the FDA and Health Canada approved only the 150 mg BID dose of dabigatran for patients with non-valvular atrial fibrillation[3]; the European Medicines Agency approved both 150 and 110 mg BID[4]. Alternative interpretations of the data shown in Table 1 are that 110 mg BID provides a net health benefit over 150 mg BID, or that this single trial has not established the optimal dose of dabigatran.

Table 2 shows key outcomes by hierarchy for the unblinded comparison between warfarin and the combined doses of dabigatran, as it is not clear which of the two doses is the best.

This analysis suggests a possible benefit of dabigatran over warfarin. Warfarin is associated with a trend toward increased mortality and increases the risk of any hospitalization by 1.6%.

However, the comparison between warfarin and dabigatran was **not blinded** and thus all outcomes are subject to performance and ascertainment bias favouring dabigatran. This interpretation is reinforced by the FDA review, which found that lack of blinding of patients and clinicians led to 'differential treatment of patients during the study period' (performance bias) and that the presence of ascertainment and adjudication bias was sufficient to overturn the claim of a stroke benefit for dabigatran 150 mg BID as compared with warfarin[2]. Furthermore the FDA clinical reviewer found that the trend toward increased mortality with warfarin was entirely due to investigator sites where INR monitoring was inferior. At sites where INR was within therapeutic range ≥ 67% of the time, relative risk for mortality (RR 1.05) favoured warfarin over dabigatran.[2]

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Table 2 shows that warfarin increased intracranial hemorrhage by 1% versus dabigatran, whereas ischemic stroke and bleeding leading to hospitalization did not differ. The NEJM report of the same data[1] is misleading because intracranial hemorrhage events contribute to most of the composite efficacy outcomes (stroke or systemic embolism, stroke, disabling or fatal stroke, hospitalization, death from vascular causes, death from any cause) and to most of the safety outcomes (major bleeding, life threatening bleeding, major or minor bleeding, intracranial bleeding and net clinical benefit outcome). Other than intracranial hemorrhage, Table 2 shows that most outcomes favor warfarin over dabigatran. Dabigatran increased myocardial infarction by 0.4%, withdrawal due to serious adverse event by 1%, and withdrawal due to any adverse effect by 4.1%.

For the RE-LY trial, the incidence of intracranial hemorrhage observed with warfarin can be annualized to a rate of 0.76% per year.

Why did warfarin increase intracranial hemorrhage 3-fold compared with the annualized rate for dabigatran of 0.27% per year? The annualized incidence of intracranial hemorrhage was lower in atrial fibrillation patients taking warfarin during comparable recent trials: 0.53% in SPORTIF III[5], 0.28% in SPORTIF V[6] and 0.3% or 0.45% in two Cochrane reviews[7,8]. These comparisons suggest something unusual about the warfarin arm in the RE-LY trial.

Additional observations

Absence of blinding in experiments creates a high risk of bias. This was amply demonstrated with ximelagatran, an earlier direct thrombin inhibitor that did not receive regulatory approval. In SPORTIF III, an unblinded clinical trial similar to RE-LY, ximelagatran was associated with numerically fewer strokes/systemic emboli versus warfarin, RR 0.71 [0.48, 1.07].[5] However, SPORTIF V, a follow-up double blinded trial, showed numerically greater strokes/systemic embolic for ximelagatran, RR 1.38 [0.91, 2.10].[6]

The use of antiplatelet agents in addition to anticoagulants was surprisingly prevalent in all 3 arms of the RE-LY trial. During the trial approximately 40% of patients took aspirin and 7% took clopidogrel at some time. Taking either antiplatelet drug doubled the incidence of major bleeding events, an absolute increase of > 2% per year. This effect was similar for both doses of dabigatran and for warfarin.

Table 2: Key outcomes for dabigatran versus warfarin

Outcome	Dabigatran 110 and 150 mg BID	Warfarin once daily	RR [95% CI]	ARR ARI
Patients randomized	12091	6022		
Deaths	890	491	0.90	
(FDA)	7.4%	8.2%	[0.81, 1.00]	
Serious adverse events	Not reported	Not reported	?	?
Hospitalizations	4741	2458	0.96	1.6%
(NEJM)	39.2%	40.8%	[0.93, 1.00]	
Intracranial hemorrhage	65	90	0.36	1%
(FDA)	0.5%	1.5%	[0.26, 0.49]	
Adjudicated Ischemic	241	118	1.02	
stroke (FDA)	2%	2%	[0.82, 1.27]	
Bleeds leading to	589	274	1.07	
hospitalization minus intra-	4.9%	4.5%	[0.93, 1.23]	
cranial hemorrhage (FDA)				
MI	176	66	1.33	0.4%
(FDA)	1.5%	1.1%	[1.00, 1.76]	
Gastrointestinal bleeds	315	120	1.31	0.6%
(NEJM)	2.6%	2%	[1.06, 1.61]	
Withdrawal due to SAE	329	105	1.56	1%
(NEJM)	2.7%	1.7%	[1.26, 1.94]	
Withdrawal due to any	2381	939	1.26	4.1%
adverse effect (FDA)	19.7%	15.6%	[1.18, 1.35]	
Any adverse effect	9449	4551	1.03	2.5%
(FDA)	78.1%	75.6%	[1.02, 1.05]	
Dyspepsia	1395	348	2.00	5.7%
(NEJM)	11.5%	5.8%	[1.78, 2.24]	

Conclusions

- **Licensing of dabigatran 150 mg BID for atrial fibrillation is premature, pharmacologically irrational and unsafe for many patients.**
- The optimal dose of dabigatran for non-valvular 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 non-valvular atrial fibrillation is required.
- **Taking antiplatelet drugs in combination with oral anticoagulants doubles the incidence of major bleeding events.**

The draft of this Therapeutics Letter was submitted for review to 60 experts and primary care physicians in order to correct any inaccuracies and to ensure that the information is concise and relevant to clinicians.

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