Post-marketing Surveillance and the Ongoing Dabigatran Controversy

Background:

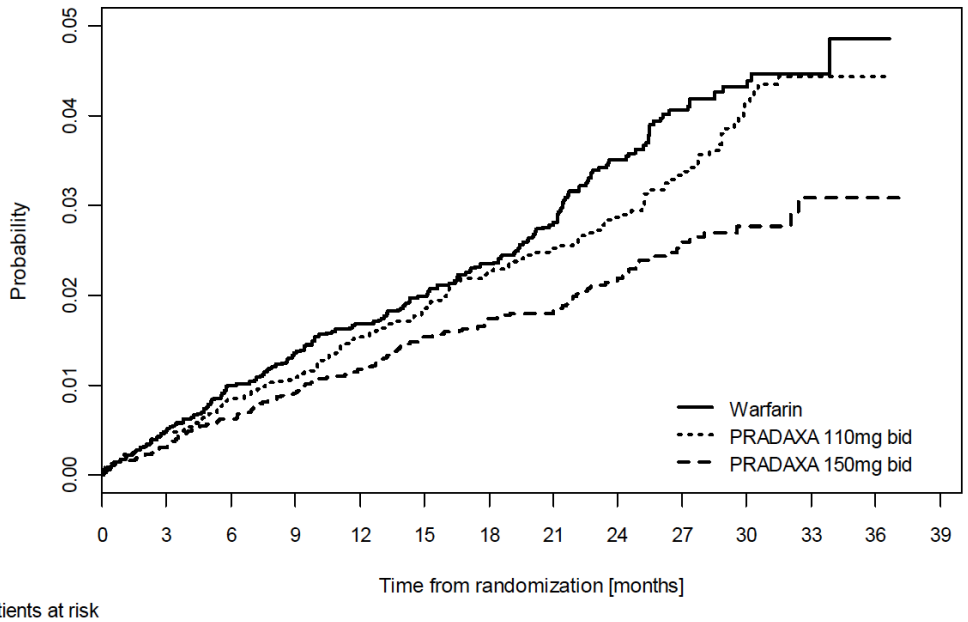
Dabigatran (Pradaxa®) is an oral anticoagulant (blood thinner) developed by Boehringer Ingelheim industries. It is used to reduce the risk of stroke or systemic blood clots in patients with atrial fibrillation. Unlike warfarin, the drug traditionally used for that indication, it does not require regular monitoring with a blood test.

In 2009 the FDA approved dabigatran as an oral anticoagulant. The decision was based largely on the results of the RE-LY trial[1,2]. RE-LY was a phase III clinical trial that randomized 18,113 patients to either warfarin or dabigatran (110 mg or 150 mg twice daily). Treatment assignment to warfarin versus dabigatran was not blinded and median duration of treatment was 2.0 years. The primary composite outcome was time to stroke or systemic embolism.

Results of the RE-LY Trial:

The incidence rate of the primary outcome in the warfarin group was 1.69% per year. When compared to the warfarin group, the rate in the group that received 110 mg of dabigatran was not significantly different (1.53% per year, relative risk = 0.91; 0.74 to 1.11). However the rate per year in the group that received 150 mg of dabigatran was significantly lower than that in the warfarin group (1.11% per year, relative risk, 0.66; 0.53 to 0.82, P < 0.001) (Figure 1).

Figure 2 Kaplan-Meier Curve Estimate of Time to First Stroke or Systemic Embolism



Patients at risk

PRAD 110	6015	5927	5862	5797	5713	5481	4615	3778	3132	2383	1446	495	87
PRAD 150	6076	6010	5940	5861	5782	5555	4700	3847	3238	2428	1481	494	90
Warfarin	6022	5937	5862	5782	5719	5438	4615	3702	3092	2338	1364	383	76

The rate of major bleeding (Table 1) was significantly lower in the 110 mg dabigatran group than in the warfarin group (p=0.003) and no difference was seen between 150 mg dabigatran and warfarin (p=0.31). The rate of intracranial bleeding was lower in both dabigatran groups than in the warfarin group (p<0.001).

Thus, the higher dose of dabigatran appeared to be more effective than warfarin with similar risk of bleeding, while the lower dose had similar efficacy but with reduced risk of bleeding.

Table 1. Safety Events, by Treatment Group (Percent Per Year)

	Dabigatran 110 mg	Dabigatran 150 mg	Warfarin
Sample Size	6076	6015	6022
Major Bleeding (% per year)	2.71*	3.11	3.36
Minor Bleeding (% per year)	13.16	14.84	16.37
Intracranial Bleeding (% per year)	0.23*	0.30*	0.74

*=significantly lower rate than in the warfarin group

Reactions from the Scientific Community:

Some members of the scientific community expressed skepticism about the FDA's decision. They called it "premature, irrational and unsafe", citing the following concerns about the RE-LY trial[3]:

- An unblinded study can be biased if patient management differs between treatment groups.
- The rate of intracranial hemorrhages was unusually high in the warfarin group when compared to other published studies.
- The number of patients taking anti-platelet agents during the trial was unusually high, leading to an increased risk of hemorrhagic episodes.
- Unlike warfarin, dabigatran does not have an antidote.

Reactions from the International Community:

Following approval of dabigatran, regulatory bodies around the world began to receive reports of bleeding events in patients treated with dabigatran and some regulatory bodies issued safety advisories:

- Japan: In August, 2011, a warning was issued about risk of severe, sometimes fatal hemorrhages in patients treated with dabigatran.
- Australia: In November, 2011 a safety advisory regarding risk of bleeding was issued. After further analysis of the reports, authorities concluded that these cases occurred during the dabigatran/warfarin transition, were mostly GI bleeds, and were associated with certain risk factors (e.g., age > 75; renal impairment; use of aspirin). They issued an advisory recommending dabigatran to be avoided in patients with these risk factors.
- Europe: In May 2012, the frequency of fatal bleeding in post-marketing data was observed to be lower for both warfarin and dabigatran treated patients than had been

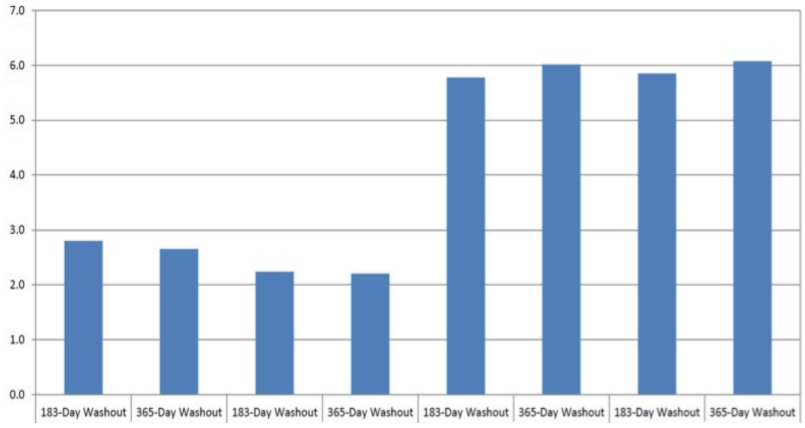
observed in the RE-LY trial.

The FDA approach:

In December 2011, the FDA responded to more than 1,700 reports it had received of bleeding events in patients taking dabigatran by initiating an investigation using post-marketing data.

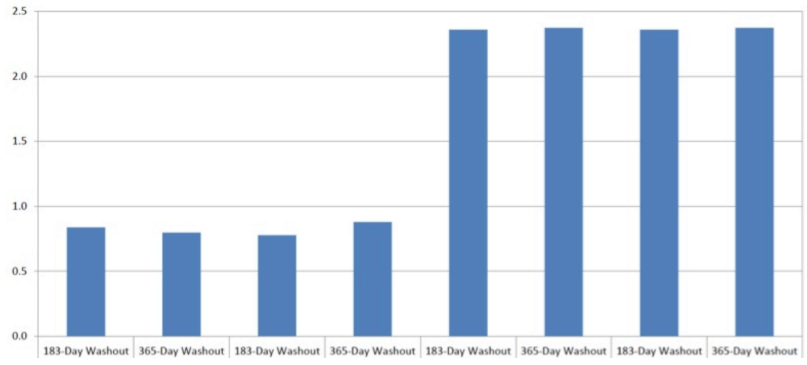
The FDA investigated both the rates of gastrointestinal bleeding (bleeding in the stomach and intestines) and intracranial hemorrhage (bleeding in the brain) for new users of dabigatran compared to new users of warfarin. The assessment used insurance claims and administrative data from the FDA's **Mini-Sentinel pilot** of the Sentinel Initiative. This investigation found that the rates of both gastrointestinal and intracranial bleeding were lower in patients taking dabigatran than in patients on warfarin using for several different definitions of the period of exposure (Figures 3 and 4).

Figure 3. New events of gastrointestinal bleeding per 100k at risk



Dabigatran Warfarin

Figure 4. New events of intracranial bleeding per 100k at risk



Dabigatran Warfarin

The FDA concluded that the apparent increased incidence of bleeding events with dabigatran was likely due to the fact that physicians were less likely to report bleeding events with warfarin, a drug whose adverse effects were well known.

In November 2012, **MedWatch** also reported that the bleeding rates with dabigatran were no higher than with warfarin. The FDA maintained drug approval and continued investigating complications and adverse events.

In April 2013, the FDA introduced a requirement for a black box warning that stopping dabigatran can increase the risk of stroke.

WARNING: DISCONTINUING PRADAXA IN PATIENTS WITHOUT ADEQUATE CONTINUOUS ANTICOAGULATION INCREASES RISK OF STROKE

See full prescribing information for complete boxed warning.

Discontinuing PRADAXA places patients at an increased risk of thrombotic events. If anticoagulation with PRADAXA must be discontinued for a reason other than pathological bleeding, consider coverage with another anticoagulant. (2.6, 5.1)

Despite the FDA analysis[4], there are currently thousands of lawsuits against dabigatran around the USA. In France, four families are suing Boehringer Ingelheim for contributing to the death of their family members.

Question:

1 – What, in your opinion, are the main limitations of the Mini-sentinel system?

2 – Given these limitations, do you think that the FDA investigation using the Mini-sentinel system provided an adequate basis for maintaining approval of dabigatran? Explain your answer.

Additional readings:

- ✓ Check the **MedWatch** warnings on Dabigatran and any other drug you wish for, on the FDA website: http://www.fda.gov/Safety/MedWatch/default.htm"
- ✓ **Mini-sentinel website**: http://minisentinel.org/assessments/medical_events/details.aspx?ID=182

1. Michael D Ezekowitz MBChB, D. *et al.* Rationale and design of RE-LY: Randomized evaluationof long-term anticoagulant therapy, warfarin, compared with dabigatran. *American Heart Journal* **157,** 805–810.e2 (2009).
2. Connolly, S. J. *et al.* Dabigatran versus Warfarin in Patients with Atrial Fibrillation. *N. Engl. J. Med.* **361,** 1139–1151 (2009).
3. Dabigatran for atrial fibrillation Why we can not rely on RE-LY. *www.ti.ubc.ca* (2011). doi:10.1002/14651858.CD001927.pub2
4. FDA Drug Safety Communication: Safety review of post-market reports of serious bleeding events with the anticoagulant Pradaxa http://www.fda.gov/drugs/drugsafety/ucm282724.htm#data