

# Pradaxa

## The Less Effective, More Dangerous Alternative to Coumadin

by Ned McWilliams and Troy A. Rafferty

**A**trial fibrillation (“AFib”), a cardiac rhythm disturbance, is a disease that affects more than two million Americans. AFib is associated with a five-fold increase risk of ischemic and hemorrhagic stroke,<sup>1</sup> making it responsible for 15 percent of the 700,000 strokes that occur in the United States each year.<sup>2</sup> Blood thinning anticoagulant medications like aspirin and Coumadin have been used for decades to reduce the risk of stroke in those with AFib. While all medications confer risks and benefits, the risk/benefit profiles of aspirin and Coumadin are considered positive and have been firmly established. Dabigatran (trade name “Pradaxa”), a drug recently approved for the prevention of stroke in patients with AFib, is being marketed by the German pharmaceutical company, Boehringer Ingelheim, as a more effective and safer alternative to Coumadin. However, contrary to these advertising claims, Pradaxa is revealing itself as less effective and disturbingly more dangerous than advertised.

Coumadin (a/k/a warfarin) has been the standard front line treatment to prevent strokes in patients with AFib for more than sixty years. Numerous well-conducted studies have established Coumadin as highly effective in reducing the risk of stroke.<sup>3</sup> However, despite the robust science supporting it, Coumadin is underutilized by those with AFib. The reason for this underutilization, estimated to be as high as 50 percent, is attributed to Coumadin’s numerous food and drug interactions, the need for frequent blood sampling and dose adjustments, and patient’s difficulty maintaining therapeutic range.<sup>4</sup> Pradaxa was designed to answer this problem of underutilization – as it was hoped that Pradaxa therapy wouldn’t require regular blood tests nor be hampered by food and drug interactions.

Pradaxa was approved for sale in the United States in October 2010. From the start, Boehringer Ingelheim engaged in a massive \$500 million promotional campaign, including 1.5 million meetings between its sales force and prescribing physicians and a TV and print direct-to-consumer advertising campaign targeting users.<sup>5</sup> As a result, more than 250,000 prescriptions for Pradaxa were written in its first six months on the market. By June of 2012, the number of prescriptions had ballooned to more than 3.2 million.<sup>6</sup> But this business success story does not have a happy ending for many who took this drug.

In the first twelve weeks Pradaxa was on the market, more than 300 serious adverse events were reported to the FDA. Within six months of hitting pharmacies and doctors’ sample cabinets, the number of adverse events skyrocketed to more than 900, including over 100 deaths. By December 2011, the number of deaths reported in users of Pradaxa had climbed to over 500.<sup>7</sup> The majority of adverse events involved internal bleeding or hemorrhaging. Taking into account the well-recognized phenomenon of underreporting,<sup>8</sup> these figures likely represent just a small fraction of the true number of serious adverse events and deaths caused by Pradaxa.

Doctors, medical researchers and regulators worldwide have now begun to unravel the mystery behind the alarming number of adverse events associated with Pradaxa. Early signs of danger came in a pre-approval clinical trial evaluating its safety and efficacy. The clinical trial that was the basis for FDA approval, The Randomized Evaluation of Long-Term Anticoagulation Therapy (“RE-LY”), compared the safety and effectiveness of Pradaxa and Coumadin. The study reported that Pradaxa was better than Coumadin “in reducing ischemic

and hemorrhagic stroke” while the risk of major bleeds was “similar with Pradaxa and [Coumadin] across major subgroups.” Disturbingly, however, the study also showed that Pradaxa had a higher risk of gastrointestinal bleeding in all patients and a higher risk of all bleeds in patients over 75 years old.<sup>9</sup>

Specifically, the study showed that patients on Pradaxa were 50 percent more likely to suffer a major gastrointestinal bleed. While Boehringer Ingelheim claims it does not know the cause,<sup>10</sup> others have hypothesized that the acid contained in the Pradaxa capsule is to blame.<sup>11</sup> Regardless of the cause, doctors are taking notice. In the March edition of the *New England Journal of Medicine*, a group of New Zealand doctors reported 78 cases of Pradaxa patients suffering bleeds within a two month period, concluding that they “are concerned that the potential risks of this medication are not generally appreciated.”<sup>12</sup>

A second explanation for the severity and number of the adverse events is the fact that, unlike Coumadin, Pradaxa has no reversal agent or “antidote.” Because of their blood thinning properties, both Pradaxa and Coumadin can cause or exacerbate bleeding events. If a patient experiences a bleeding event while on Coumadin, health care providers have a host of options available that allows them to reverse the blood-thinning effects. This allows health care providers to prevent what would otherwise be a fatal bleeding event or reverse the effects of Coumadin enough to allow surgical intervention without the risk of causing further blood loss. But because of its design and mechanism of action, Pradaxa’s blood-thinning effects cannot be reversed. Making matters worse, the lack of a reversal agent was not disclosed in the warning section of the Pradaxa drug label until January 2012, and to date has not been disclosed in the numerous and widespread advertisements for this new medication.

Also, unlike Coumadin, Pradaxa’s blood-thinning effects cannot be monitored. So in the event where a health care provider discontinues Pradaxa in a bleeding patient, they have no way of knowing when surgical intervention can be safely conducted.

The lack of a reversal agent and the inability to monitor Pradaxa is causing concern among health care professionals. The March 2012 edition of *Emergency Medical News* raised this issue wherein Dr. Mark Mosley wrote “[p]erhaps the largest piece of data missing from this study [RE-LY] (and any ads) is that [Pradaxa] cannot be reversed. This raises huge questions concerning elective surgeries, emergent procedures, GI bleeds, nosebleeds, and head bleeds for patients taking it.”<sup>13</sup> Similarly, in a letter to the editor of the *New England Journal of Medicine*, Dr. Bryan Cotton, et al., wrote that the “lack of a readily available method to determine the degree of anticoagulation created a major challenge to those treating injured patients. Moreover, the irreversible coagulopathy of [Pradaxa] is of great concern to trauma and emergency physicians.”<sup>14</sup>

This all begs the question: why was this drug ever approved? The answer lies in the fact that the makers of Pradaxa claim their drug is more effective than Coumadin, and therefore worth the additional risks of bleeding and the lack of an antidote. This rationale of course assumes that Pradaxa is better than Coumadin. But what if it isn’t? There is mounting evidence that this is not the case.

Boehringer Ingelheim’s national advertising for Pradaxa claims a 35 percent reduction in the risk of stroke compared to Coumadin. Some contend this is a misleading statistic. The RE-LY study had more than 18,000 patients with AFib. The patients on Pradaxa had a stroke rate of 1.11 percent. The patients on Coumadin had a stroke rate of 1.69 percent, an *absolute difference of 0.58 percent*. Rather than include this 0.58 percent absolute risk reduction figure in their TV commercials, the makers of Pradaxa are promoting the seemingly more impressive 35 percent relative risk.<sup>15</sup>

Physicians and regulators are beginning to question whether this minimal “benefit” is worth the added risk of Pradaxa. Dr. Cotton, et al., wrote that “although an absolute reduction [...] in intracranial hemorrhage may be statistically significant (in 18,000 patients), this may not be clinically meaningful.” Similarly, the United Kingdom equivalent of the FDA stated that “evidence was presented [...] indicating that people [well controlled with Coumadin] may not gain additional clinical benefit by taking [Pradaxa].”<sup>16</sup>

Doctors and regulators are expressing these concerns while operating under the belief that the results of RE-LY are accurate, but there are reasons to question the integrity of the RE-LY clinical trial. Unlike the studies that established the effectiveness of Coumadin, the RE-LY study was not double blinded, nor was it placebo controlled. By conducting this study in an unblinded fashion, both the investigators and the patients enrolled in the study knew which medication was being administered. This is well known to bias results of clinical studies. As the Australian FDA noted, “the [RE-LY] study was a PROBE design. As PROBE designs are open-label rather than double-blind they are subject to bias.”<sup>17</sup> In an effort to control for this bias, Boehringer blinded a panel of adjudicators who determined whether patients suffered a stroke, a bleeding event or other negative outcome. But an FDA audit of RE-LY discovered that up to 20 percent of the records reviewed by the panel of adjudicators contained information that could unblind them as to which medication the patient was taking.<sup>18</sup> The FDA was therefore left to take the investigators at their word that they didn’t review the information that would have revealed which drug a particular patient was assigned.

This raises yet another concern with the study and those who conducted it: funding bias. It is well recognized that studies funded by the manufacturer of a drug disproportionately favor the study drug compared to studies that are independently funded.<sup>19</sup> Not only was RE-LY funded by Boehringer Ingelheim, but 18 of the 20 named authors of the RE-LY study disclosed a financial conflict of interest with Boehringer Ingelheim.<sup>20</sup>

In addition to the questionable study design, sloppy “blinding,” and the potential for bias, there were numerous data integrity issues associated with RE-LY. The FDA audit identified dozens of bleeding events that were not properly reported initially, leading the FDA reviewer to conclude that “the frequency of errors in the data sets impedes our ability to perform an adequate review, and undermines our confidence in [the] data.”<sup>21</sup> Similarly, the Australian FDA stated that “it was of concern that such a large number of major bleeds were not initially identified in the original study and this suggests a significant problem with initial quality control and/or auditing of the study.”<sup>22</sup>

While the FDA ultimately accepted the revised results of RE-LY, the agency remained concerned about the integrity of RE-LY due to the fact that Boehringer Ingelheim altered the design of the study *after most of the data had been collected. Specifically, the FDA reviewer stated that “consideration should be given to the late date at which the statistical analysis plan was finalized (essentially after all of the study data has been amassed)” as the agency had previously “expressed significant concerns about the changes given the amount of information that was available to influence the decision to alter the statistical analysis plan.”*<sup>23</sup> At a September 20, 2010, meeting, the same FDA reviewer testified that “you just get a little bit uneasy when things aren’t finalized until later. You sort of, not saying that someone knew something here and changed something, *but there is a sense of who knew what and when.*”<sup>24</sup>

Some medical professionals are being less diplomatic in the language they use to describe RE-LY and its findings. In an article titled “Why we cannot rely on RE-LY”, a group of 60 experts and physicians wrote that the data published in RE-LY was “misleading,” the sale or prescription of Pradaxa is “premature, pharmacologically irrational and unsafe for many patients,” and that “an independent audit of RE-LY is needed to check for irregularities in conduct [and] sources of bias.”<sup>25</sup> Similarly, Dr. Mosley stated that “until better studies can be done, including head to head comparisons with other new anticoagulants, we should not be using [Pradaxa].”

Despite the concerns from the actual scientists at the FDA who reviewed the data, including their recommendation that “a superiority claim over [Coumadin] should not be granted,”<sup>26</sup> incredibly, the FDA not only approved Pradaxa for sale, but allowed Boehringer Ingelheim to claim (and advertise) that their product is more effective than Coumadin. Making matters worse, doctors and users are being misled into thinking Pradaxa is safer than Coumadin due to the fact that Coumadin has the dreaded “black box warning” about the risk of bleeding, while Pradaxa does not – despite the fact the risk of bleeding with Pradaxa is the same or worse than Coumadin.

Boehringer Ingelheim’s promotional efforts appear to be effective. In April 2012, Boehringer Ingelheim announced that Pradaxa had achieved the revered “blockbuster” status – celebrating annual sales in excess of \$1 billion. Perhaps it should come as no surprise that the number of serious adverse events and deaths reported in Pradaxa users continues to rise.

### Litigation Update

As of June 1, 2012, twenty cases have been filed in nine federal courts. Additionally, two cases have been filed in state courts, including Connecticut, the base for Boehringer Ingelheim’s U.S. operations. A petition seeking Multidistrict Litigation (“MDL”) status was filed with the United States Judicial Panel on Multidistrict Litigation (“JPML”) on May 30, 2012. The next JPML hearing is scheduled for July 26, 2012. A decision from the panel on the status and location of a Pradaxa MDL is expected by the end of August 2012.

<sup>1</sup> Rosamond W, Glegal K, Furie K, Go A, Greenlund K, Haase N., et al. Heart disease and stroke statistics – 2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics

Subcommittee. *Circulation* 2008; 117(4): e25-e146

<sup>2</sup> Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham study. *Stroke* 1991; 22: 983-988

<sup>3</sup> Hart RG, Benavete O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med* 1999; 131(7):492-501

<sup>4</sup> Friberg L, Hammar N, Ring M, Pettersson H, Rosenqvist M. Stroke prophylaxis in atrial fibrillation: who gets it and who does not? (SCAF-study). *Eur Heart J* 2006; 27(16): 1954-1964

<sup>5</sup> Deborah Weinstein, Study: Sales Support is Dwindling, Not Dead, March 14, 2012, Medical Marketing and Media

<sup>6</sup> BI June 6, 2012, Press Release (PR Newswire)

<sup>7</sup> <http://ismp.org/QuarterWatch/pdfs/2011Q4.pdf>

<sup>8</sup> Hazell L, Shakir SA. Under-reporting of adverse drug reactions: a systematic review. *Drug Saf.* 2006;29(5)385-96

<sup>9</sup> <http://www.prnewswire.com/news-releases/pradaxa-dabigatran-etexilate-mesylate-us-label-now-affirms-superior-reduction-in-ischemic-and-hemorrhagic-stroke-versus-warfarin-in-patients-with-non-valvular-atrial-fibrillation-157449775.html>

<sup>10</sup> <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM233739.pdf> pg. 78-79

<sup>11</sup> Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361:1139-51.

<sup>12</sup> Harper P, Young L, Merriman E. Bleeding Risk with Dabigatran in the Frail Elderly. *N Engl J Med* 2012;366:9 864-866

<sup>13</sup> [http://journals.lww.com/em-news/Fulltext/2012/03151/Viewpoint\\_\\_Why\\_EPs\\_Should\\_Avoid\\_Dabigatran.1.aspx](http://journals.lww.com/em-news/Fulltext/2012/03151/Viewpoint__Why_EPs_Should_Avoid_Dabigatran.1.aspx)

<sup>14</sup> *NEJM* 365;21 (November 24, 2011)

<sup>15</sup> [www.pradaxa.com](http://www.pradaxa.com)

<sup>16</sup> <http://publications.nice.org.uk/dabigatran-etexilate-for-the-prevention-of-stroke-and-systemic-embolism-in-atrial-fibrillation-ta249/consideration-of-the-evidence>

<sup>17</sup> [www.tga.gov.au/pdf/auspar/auspar-pradaxa.pdf](http://www.tga.gov.au/pdf/auspar/auspar-pradaxa.pdf)

<sup>18</sup> <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM233739.pdf> pg. 115-116

<sup>19</sup> Baker, C. Bruce, et al., *Quantitative Analysis of Sponsorship Bias in*

*Economic Studies of Antidepressants. British Journal of Psychiatry 183: 498-506, 2003*

<sup>20</sup> Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361:1139-51.

<sup>21</sup> [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2010/022512Orig1s000Admin.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022512Orig1s000Admin.pdf)

<sup>22</sup> [www.tga.gov.au/pdf/auspar/auspar-pradaxa.pdf](http://www.tga.gov.au/pdf/auspar/auspar-pradaxa.pdf)

<sup>23</sup> <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM247244.pdf>

<sup>24</sup> <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM233739.pdf>

<sup>25</sup> Therapeutics Initiative Evidence Based Drug Therapy; Dabigatran for atrial fibrillation why we can not rely on RE-LY; March 2011

<sup>26</sup> <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM247244.pdf> pg. 14



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