

# ANALYSIS

## Dabigatran, bleeding, and the regulators

**Thomas J Moore and colleagues** highlight the differences in how US and European regulators managed the safety problems of the new anticoagulant dabigatran and ask both to think again and mandate plasma monitoring of dabigatran

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Dabigatran was the first drug across the finish line in the global race to develop a new and better replacement for the five decade old anticoagulant warfarin. An important indication was long term treatment to reduce the risk of stroke in patients with non-valvular atrial fibrillation. This vulnerable older group, mostly over age 75, number many millions worldwide. The main risk of treating atrial fibrillation with warfarin is that inhibiting coagulation can also result in bleeding in the brain, eyes, intestines, and elsewhere. A major bleed after warfarin treatment could result in patients losing 20-30% of their blood supply before the bleeding was halted. However, the objective of treatment was also important: blood could pool and form clots in the fibrillating atrial primer pumps, and these clots could travel to the brain, lungs, or elsewhere, causing irreversible damage.

As regulators at the European Medicines Agency (EMA) and US Food and Drug Administration (FDA) considered the benefits and risks of dabigatran in 2010, they knew, or should have known, that reducing risk of bleeding with anticoagulants deserved to be ranked as a patient safety issue of the first order. A study of cases of drug adverse effects seen in 58 emergency departments across the United States<sup>1</sup> showed that warfarin accounted for more emergency hospital admissions in patients aged 65 or older than any other drug. Warfarin accounted for 33.3% of all hospital admissions from the emergency department for adverse drug effects; insulins were next with 13.9%.

The two agencies' evaluation of dabigatran was a study in contrasts. The FDA pursued a policy making the new drug easier to use with just one primary dose, even though it would increase the risk of haemorrhage in older patients. But the FDA also believed its actions might slightly improve the efficacy of dabigatran in preventing stroke. The EMA, by contrast, showed continuing concerns about reducing the risk of bleeding and pursued multiple risk reduction policies. But neither agency insisted on the most effective step to reduce bleeding risk—optimising the drug's anticoagulant effect in each patient.

### Single pivotal clinical trial

Most data supporting the US and European approval of dabigatran for non-valvular atrial fibrillation came from a single non-inferiority trial (n=18 113) comparing dabigatran with warfarin.<sup>2</sup> Known as RE-LY and published in 2009, it compared two fixed doses of dabigatran, 110 mg twice daily and 150 mg twice daily, with warfarin at a dose adjusted for each patient to optimise anticoagulation. The study had 18 different endpoints or combinations of endpoints, divided roughly equally between efficacy (primarily stroke and other thromboembolic events) and safety (mainly various definitions of bleeding).

Most absolute differences between dabigatran and warfarin were less than 1% a year. For example, compared with warfarin 150 mg dabigatran reduced ischaemic strokes by 0.28% (1.2% v 0.92%) and major bleeds by 0.25% (3.36% v 3.11%) but increased the number of myocardial infarctions by 0.21% (0.53% v 0.74%). Because of the large sample size most of these small differences were statistically significant. However, with a largely unblinded trial in 951 centres spread across 44 countries, it was not clear whether differences of a fraction of 1% a year were clinically relevant.

If the differences between dabigatran 150 mg twice daily and warfarin were quite small, the absolute bleeding risks of both drugs in this patient population were quite large (table 1). In the published, corrected, adjudicated version, major bleeding rates ranged from 2.87% a year with dabigatran 110 mg to 3.57% with warfarin.<sup>3</sup> The definitions for "major bleeds"—set years earlier for testing drugs with haematological effects—were limited to the most severe bleeds and could exclude emergency room visits, symptomatic gastrointestinal bleeding that didn't require a two unit transfusion, and some emergency admissions.<sup>4</sup> In the RE-LY trial, major and minor bleeds occurred in 18.5% of warfarin patients each year and 16.4% of patients taking dabigatran 150 mg twice daily.

The question, then, was what advantages the newly developed dabigatran might have over warfarin, the standard treatment in atrial fibrillation for decades? The answer from the manufacturer, Boehringer Ingelheim, was ease of use. Warfarin requires monitoring as often as twice a month. It needs not only initial dose adjustments to achieve optimal effect on blood clotting but also continued monitoring because the drug's effect on coagulation varies over time. But the company claimed that no monitoring of plasma levels was required for dabigatran.<sup>5</sup> In 2010, it proposed dose reduction to reduce the risk of bleeding in patients aged 80 and older.

## Variation in plasma concentrations

Although results were not published until late 2013, the RE-LY trial had included a large sub-study (n=9183) that raised serious questions about whether patients taking dabigatran needed plasma level testing to reduce the risk of bleeding or clotting and to ensure maximum benefit from the drug.<sup>6</sup> The RE-LY sub-study showed a fixed dose of dabigatran had wide variability in plasma levels that were directly related to risk of bleeding. After a month of treatment, the 150 mg twice daily dose could produce peak plasma levels as low as 2.3 ng/mL and as high as 1000 ng/mL. A conservative measure that omitted 20% patients at the extremes and used log transformed data indicated a 5.5 fold variability. Dabigatran's high variability was not a desirable characteristic for a drug where not enough anticoagulation means loss of benefit in stroke prevention and too much anticoagulation increases the risk of haemorrhage.

The variability is explained by the basic pharmacology of dabigatran. It combines low bioavailability (3-7%), two metabolic steps to convert the pro-drug into the active drug, and a single primary route of elimination (the kidneys).<sup>7</sup> As a result, a small difference in metabolic activation or kidney function could have a large effect on plasma level and bleeding risk. These properties were not shared by two new indirect thrombin inhibitors, apixaban and rivaroxaban, which have much higher bioavailability (50-80%) and multiple routes of elimination.<sup>8,9</sup> The figure↓ shows a company model of dabigatran exposure-outcome data based on the RE-LY sub-study results for a median duration of two years.<sup>6</sup> As the company has stated, dabigatran showed a wide therapeutic range in effects on stroke, with roughly similar efficacy from around 50 ng/mL through 300 ng/mL. But the probability of major bleeding rises rapidly, from around 2-3% at 50 ng/mL to more than 9% for the typical patient around 300 ng/mL, and to more than 12% at the extremes.

The company solution to the plasma level variability/bleeding risk problem was limited dose adjustment based on patient characteristics rather than patient plasma levels. It recommended that FDA regulators approve the 110 mg dose for patients 80 years and older.<sup>5</sup> The company concluded that the drug should not be used in patients with severe kidney impairment, defined as creatinine clearance  $\leq$  30 mL/min.

## FDA approval

The FDA initially refused to process the application to approve dabigatran after detecting numerous data quality problems in the RE-LY trial.<sup>10</sup> After a resubmission, it conducted a multidisciplinary review, completed its own pharmacokinetic and pharmacodynamic modelling, and held an advisory committee review with outside experts. Marketing approval came in October 2010.

The record shows that FDA senior managers chose to disregard the increasing risk of bleeding with increased plasma levels. Not only did the agency reject a Boehringer proposal to recommend the lower 110 mg twice daily dose in patients 80 years old, it rejected the lower dose entirely. "Approval of the 110-mg strength would provide the average patient with the option of taking a dose with lower efficacy, leading to additional strokes and disability. One could attempt to discourage this behavior through education, but that strategy might not prove very effective," wrote a senior FDA manager in the official approval decision document.<sup>10</sup> "There is a danger that the 110 mg dose would be over utilized if approved." To knowingly expose thousands of older patients to an avoidable risk of bleeding because of an opinion that physicians were not capable of making accurate clinical assessments is an unusual basis for a regulatory decision.

## New formulation

The FDA not only wanted to limit physicians to the higher 150 mg strength, it raised no objections when the company sought approval to market a new formulation that increased the dose to around 165 mg. The data also showed that 10% of patients would get an even larger dose—26% higher or more. For comparison, the company had reported a 38% difference in peak plasma levels between the 110 and 150 mg twice daily doses.<sup>6</sup> An internal Boehringer document made public in civil litigation had this assessment from its product team: "The only reason the [FDA] Division accepted the BE [bioequivalence] study for the new formulation was that the dose was greater than 150—around 165 mg. They firmly believe higher dabigatran concentrations are better."<sup>11</sup> Given that efficacy in stroke prevention was relatively insensitive to dose, and bleeding risk increased continually with dose, this change had an unfavourable effect on the drug's safety profile. The prescribing information for physicians did not reveal that the strength they would use in patients was higher than used in the RE-LY clinical study.<sup>7</sup> In a final and unusual step, the FDA instructed Boehringer to introduce a 75 mg twice daily dose that had not been tested in people with atrial fibrillation and indicated it for use in patients with severe kidney impairment, who had been excluded from the dabigatran trials for safety reasons.<sup>7,10</sup> The FDA concluded "it was desirable to provide access" for this patient population.<sup>10</sup>

## Input from outside advisers

An FDA advisory committee opposed the agency's decision to reject the 110 mg dose and questioned the lack of data on patients with severe kidney impairment.<sup>12</sup> The decision had evidently been made before the committee met in September 2010 because the agency did not schedule an official vote on the 110 mg dose. (The FDA specifies the questions that the committee can officially consider.) However, the chairman insisted on an unofficial vote for the record. Despite the FDA management's advocacy of a single dose, the vote was 6-4 in favour of making the lower dose available.

One member of the advisory committee also focused on the question that was otherwise not even on the table: With such high plasma level variability, didn't dabigatran really need plasma level monitoring?

"I'm struck by what my eyeball tells me about a five-fold variability within the 90 percent confidence [interval] of the 150-dose. That seems awfully big to me in a drug that we're proposing to use without therapeutic monitoring," said Darren McGuire, a cardiologist on the panel.<sup>12</sup> An agency

pharmacologist told him, “We didn’t see a need for monitoring the concentration because we saw in a study, a favorable result in all subgroups.”

Another committee member, Jonathan C Fox, asked about the 75 mg dose for severe kidney impairment. “If I read the documents correctly it seems there is little to no data at all.”<sup>12</sup> He was told that the FDA recommendation was result of modelling at the behest of senior management; Boehringer said use in severe kidney impairment should be contraindicated.

Thus the FDA approved dabigatran with only the 150 mg strength except for patients with severe kidney impairment. The indication was also broad, for any patient with “non-valvular atrial fibrillation.” It left physicians without a viable option to reduce risk of bleeding even in the oldest patients. With a single dose for most patients and no monitoring of plasma levels, it was certainly going to be easy to use.

The FDA showed a strange tunnel vision in pursuing a reduction in stroke rates of a fraction of 1% on the basis of a single trial whose data quality the agency had already challenged. Its model of the trade-offs between stroke and bleeding focused on fatal and life threatening bleeds, which excluded 91% of bleeds in RE-LY.<sup>12</sup> The cost of these decisions was sometimes doubling or tripling the risk of severe bleeding in older patients, patients with impaired kidney function, low body weight, those who were taking aspirin, or who for other reasons ended up with excessively high plasma levels.

## EMA focuses on bleeding

In contrast to the FDA, from the onset the EMA reviewers focused on actions to minimise the bleeding risks of dabigatran. The EMA approval process for dabigatran for non-valvular atrial fibrillation took longer (18 months v 9 months) and involved more interactions with Boehringer Ingelheim for additional data or to resolve questions.<sup>13</sup> The EMA review also differed because the agency had already approved dabigatran in 2008 for a more limited medical use, preventing venous thromboembolism after hip or knee replacement.<sup>14</sup>

EMA rapporteurs reviewed and expressed concern about the large variability in plasma levels and bleeding risk found in the then-unpublished RE-LY sub-study data. EMA requested, received, and published a therapeutic range (48-200 ng/mL). It also ensured that an accurate assay was available and validated, the Hemoclot direct thrombin inhibitor assay.<sup>15</sup> But the EMA did not oppose Boehringer’s global plan to market dabigatran as an alternative to warfarin that did not require blood level testing to establish the optimal level of anticoagulation.

The EMA not only approved the lower 110 mg dose to reduce bleeding risk but enlarged the patient population for which it was recommended, reducing the age from the 80 years proposed by the company, to 75 years in patients with additional risk factors. It restricted the indication to atrial fibrillation patients at higher risk for stroke rather than all patients with non-valvular atrial fibrillation. And it contraindicated use in patients with severe renal impairment, the population for which the FDA had created the untested 75 mg dose. In addition, the EMA required Boehringer to conduct an education programme for doctors on how to monitor kidney function and reduce bleeding risks, and specified that patients receive an alert card. The EMA approved dabigatran for non-valvular atrial fibrillation in high risk patients in August of 2011. However, within months new signals about bleeding were being observed from postmarketing reports in the US, Japan, and other countries where dabigatran had been approved earlier.

## Reported deaths after approval

By December of 2011 regulators in the United States, Europe, and Japan were learning about thousands of postmarketing adverse event reports of serious and fatal bleeding, mainly in older patients taking dabigatran in the United States at the 150 mg dose. The FDA published a notice that it was reviewing cases,<sup>16</sup> and the EMA asked the manufacturer for a detailed tabulation of all reported deaths from bleeding.<sup>17</sup>

The EMA assessment,<sup>17</sup> a company internal study,<sup>18</sup> and an independent outside review<sup>19</sup> all told the same story. Serious bleeds and deaths were occurring in older patients, median age of 80. Where details were known, data showed 26.1% of fatal bleeds were occurring within 10 days of starting treatment, and 67.8% within the first 30 days. Spontaneous adverse event reports (MedWatch reports in the US, Yellow Card Scheme in the UK) do not provide reliable estimates of how frequently bleeds were occurring, but they do provide a profile of the affected patients. As of December 2011, the company summary cited 9049 reported bleeding events in its global experience, including 368 deaths.<sup>18</sup>

Why were so many dabigatran bleeds being reported? Data now publicly available on plasma concentration of dabigatran in RE-LY participants provides one answer.<sup>6</sup> At least 10% of patients had peak plasma level concentrations  $\geq 383$  ng/mL when taking the 150 mg dose. This is about seven times (48-50 ng/mL) the minimum level needed for stroke prevention, according to the company.<sup>20</sup> Other factors could increase bleeding risk further. The EMA concluded that concomitant therapy with antiplatelet agents such as aspirin or clopidogrel roughly doubled bleeding risk with either dabigatran or warfarin.<sup>13</sup> And the 12% stronger reformulation that was being prescribed by doctors increased the risk of bleeding beyond the rates reported in the RE-LY sub-study.

## FDA response

The FDA’s primary response to the bleeding reports was to launch an observational study comparing warfarin with dabigatran using its pilot postmarket surveillance system called Mini-Sentinel ([www.mini-sentinel.org](http://www.mini-sentinel.org)) rather than traditional postmarket adverse event reports. Mini-Sentinel could be used to access insurance claims data for more than 120 million persons, but the data had many drawbacks for drug safety analysis, such as limited patient medical information. The FDA review took 11 months, with partial results published online in November 2012<sup>21</sup> and crucial details such as event totals and interpretation published in the *New England Journal of Medicine* in March 2013.<sup>22</sup> The FDA conclusion was, “The Mini-Sentinel assessment suggests that bleeding rates associated with dabigatran are not higher than those with warfarin.” It did not publicly characterise or analyse the thousands of adverse event reports and dismissed them as “a salient example of stimulated reporting.”<sup>22</sup> The quality of the FDA study was soon questioned.<sup>23 24</sup> Because the surveillance period ended too soon after the approval of dabigatran, the study had captured only 19 cases of gastrointestinal haemorrhage with dabigatran, and the claims data lacked information about age or sex, which are two established risk factors.

## EMA considers mandatory testing

The EMA, on the other hand, considered whether to require plasma level testing for dabigatran.<sup>17</sup> The EMA had already obtained a therapeutic range from Boehringer Ingelheim, 48-200 ng/mL, which was included in the EU approved product

information. An ad hoc advisory committee of experts met in March 2012 to consider whether to require testing and whether additional safety measures to reduce bleeding risk were required.

The company presentation to the committee stated, "routine monitoring of the anticoagulant activity is not necessary." The meeting minutes show the company position was accepted and no further action was recommended on monitoring, although the vote was divided.<sup>25</sup> However, a review of the EMA meeting materials shows that the company slide presentation did not include all their relevant data on plasma level variability of dabigatran. Because of the statistics it elected to present, the plasma level variability appeared to be about 2.3-fold instead of 5.5-fold as later published in the RE-LY sub-study.<sup>26</sup> Even the 5.5-fold variability excluded 20% of the patients at the extremes. The committee, however, did recommend, and the EMA later approved, some clarifying technical language on other concerns in the 146-page official product information "to diminish the risk of bleeding events."

## Risks and benefits of 110 mg dose

By 2014, substantial evidence from several sources showed that selective use of 110 mg dabigatran could reduce serious bleeding without loss of efficacy in preventing strokes. A company funded analysis compared the two doses of dabigatran on ischaemic and haemorrhagic strokes combined and concluded "there were no significant differences in ischemic stroke equivalents between doses."<sup>27</sup> The published sub-study of RE-LY concluded, "Individual benefit-risk might be improved by tailoring dabigatran dose."<sup>26</sup> A pharmacovigilance study in Denmark showed that doctors prescribed conservatively; 82% of patients aged 75 or older and 97% of patients aged 80 or older received the 110 mg dose.<sup>28</sup> Nevertheless, investigators reported similar stroke/systemic embolism rates at both doses, and favourable rates compared with warfarin.

The EMA examined a subset of spontaneously reported deaths from bleeding in which dose was known. It concluded that 23.1% of deaths occurred in patients receiving the 150 mg dose who would have received a lower dose under its guidelines.<sup>17</sup> The FDA's decision to decline the 110mg dose meant tens of thousands of older patients were being exposed to increased risks of severe bleeding.

## Risk of undertreatment

In 2012, a second risk of dabigatran became visible. At the low end of the variability range, plasma levels in some patients were insufficient to reduce the risks of stroke and other thromboembolic events. When Boehringer planned a new clinical trial for patients with mechanical heart valves, it opted to individualise the dose for each patient to insure optimum anticoagulation. It selected a minimum of 50 ng/mL to be effective. The company revealed in its study plan that 17% of RE-LY patients had ended up with plasma levels that were lower than 50 ng/mL.<sup>20</sup> The heart valve study using dose adjustment showed that at least 8% of participants had plasma levels below the 50 ng/mL target even when prescribed double the maximum approved dose—up to 300 mg twice daily. The investigators concluded that these patients would need anticoagulation with a different drug.<sup>29</sup> For reasons apparently unrelated to the dose adjustment, the dabigatran study in mechanical heart valves was stopped for safety, and its use in this patient population promptly contraindicated in both the EU and US.

## Benefits of plasma level adjustment

The most detailed known investigation of plasma level adjustment was a Boehringer unpublished simulation model. It was based on the RE-LY sub-study and released during US litigation proceedings.<sup>30</sup> It compared the 150 mg dose twice daily required in the United States with a hypothetical treatment programme in which dose would be optimised for each patient to achieve a plasma concentration of 90-140 ng/mL. The model showed that only 45% of patients would receive the 150 mg standard starting dose; 26% should be reduced to 75 mg and 30% to 110 mg. The model projected that major bleeding could be reduced by 20% compared with the 150 mg dose without having a statistically significant effect on rates of ischaemic stroke and serious embolism, although the actual number of events was slightly higher with the adjusted dose. Compared with warfarin the hypothetical reduction in risk of major bleeding was 40% and the risk of stroke or serious embolism was not statistically different, although there were slightly fewer events with dabigatran. These results showed substantial benefits in adjusting dose to optimise the level of anticoagulation in each patient. Most patients could benefit from a lower dose and reduced bleeding risk with no loss of efficacy. Other data showed an additional 8-17% of patients would be identified as not getting enough anticoagulant effect to optimally prevent strokes and could be switched to another drug.

Despite this growing accumulation of evidence that bleeding risk could be reduced, the FDA continued to insist on a 150 mg dose except in severe renal impairment. It neither required nor published postmarket studies of treatment outcomes in the untested 75 mg dose in severe kidney impairment. Monitoring kidney function was "recommended" but of limited value without a lower dose. The Hemoclot plasma level assay was not available in the US except for research use (Aniara Diagnostica, personal communication).

In May 2014, the FDA announced a few results of an expanded observational study comparing dabigatran with warfarin.<sup>31</sup> Although not providing basic information about the number of events, dose, or patient characteristics, the FDA reported that compared with warfarin, dabigatran resulted in 0.26% fewer strokes, 0.6% fewer intracranial haemorrhages, and 0.77% more gastrointestinal bleeds. The limited data reported looked similar to those from the RE-LY trial. "We have made no changes to the current label or recommendations for use," the FDA said.

## More action needed

The safety of dabigatran in non-valvular atrial fibrillation can be substantially improved in both the US and EU. The manufacturer, the FDA, and EMA need to agree on a therapeutic range and recommend initial dose adjustment based on plasma measurements. The plasma level test needs to be available in the US. The FDA should make available the lower 110 mg strength that is approved in the EU, Canada, New Zealand, and Australia to permit dose adjustment in high risk patients. Finally, regulators should recommend plasma level testing in all new patients, and eliminate the recommendation dabigatran "does not in general require routine anticoagulant monitoring."

Though this analysis has focused on optimising the safety of dabigatran, ten Cate argues persuasively<sup>32</sup> that the safety of all the new anticoagulants can be potentially improved through documenting a therapeutic range for each agent, individualising dose in many patient subsets, and improving adherence.

### Key messages

- Anticoagulation treatment in non-valvular atrial fibrillation is one of the highest risk outpatient treatments in older patients, causing bleeding in more than 15% patients treated for a year
- With a 5.5-fold variation in plasma levels, the bleeding risk of dabigatran can be reduced and efficacy improved by individualising the dose in patients based on plasma level, age, and kidney function
- The European Medicines Agency makes information, tests, and varying strengths of dabigatran available to promote safer use
- The US Food and Drug Administration focused on efficacy rather than reducing bleeding risk, allowed only a single primary therapeutic dose, and has not approved a plasma level diagnostic test

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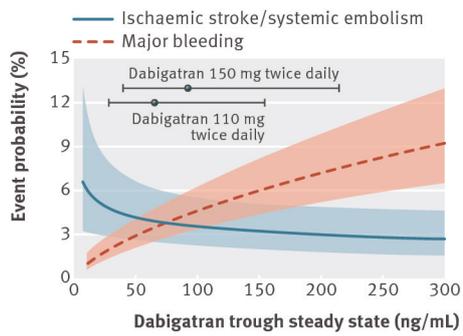
## Table

Table 1 | Major bleeds in RE-LY trial defined by different criteria\*

	No (%) taking dabigatran		No (%) taking warfarin (dose adjusted)
	110 mg twice daily	150 mg twice daily	
Major bleeds	377	460	451
Hospital admission required	275 (73)	358 (78)	345 (77)
Transfusion $\geq$ 2 units	229 (61)	304 (66)	238 (53)
Gastrointestinal bleed	150 (40)	209 (45)	132 (29)
Symptomatic intracranial bleed	31 (8)	36 (8)	85 (19)
Surgical intervention required	35 (9)	56 (12)	62 (14)
Died	26 (7)	28 (6)	39 (9)

\*Excerpted from EMA Rapporteur Day 80 critical assessment report<sup>13</sup>

## Figure



Company model of effect of dabigatran according to trough concentrations in patients taking 110 mg or 150 mg twice daily doses with 10th and 90th percentiles<sup>6</sup>