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FEATURE

ANTICOAGULANTS

Concerns over data in key dabigatran trial

Deborah Cohen considers the evidence that there may be a higher risk of bleeding with dabigatran than has previously been reported

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One of the key selling points of the new oral anticoagulant dabigatran for use in stroke prevention in non-valvular atrial fibrillation is that the drug requires no time consuming anticoagulant activity or drug plasma level monitoring. But the evidence on which these claims were based has been called into question by the publication of new material as a result of an investigation in *The BMJ*.[1]

Documents released during US litigation and those obtained through freedom of information show how Boehringer Ingelheim, the makers of dabigatran, failed to share with regulators information on how monitoring plasma levels of the drug and subsequent dose adjustment could reduce risk of major bleeds.

Boehringer, maintains, however, that the anticoagulant activity or plasma concentrations of dabigatran do not need to be monitored.

"Our scientists determined, and the Food and Drug Administration concurred, that the research does not support making dosage decisions based on plasma concentrations—a conclusion based solely on science and patient welfare," a spokesperson told *The BMJ*.

Nevertheless there is evidence that there is a potentially higher bleeding risk with dabigatran than has been stated in publications of the single clinical trial used for regulatory approval and indeed, was previously stated to the regulators.

Right from the start the design and oversight of the only key trial, the RE-LY trial, was poor. Writing in the Canadian independent drugs bulletin *Therapeutics Letter* in early 2011, academics issued concern over many aspects of the trial. "[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," they said.[2] Earlier this year authors of a meta-analysis investigating the risk of intracranial haemorrhage with new oral anticoagulants said that primary investigators should make patient level data "public for the interest of scientific rigor."[3]

Now further questions have emerged that cast doubt on the validity of the reported outcomes.

The BMJ has learnt that it has taken three reviews of the data to calculate the number of major and fatal bleeds among trial participants, and even today there are doubts whether all events have been properly accounted for.

However, the number of bleeds is a key selling point for dabigatran. In March 2012, documents released during US litigation show the company started to develop marketing messages for drug representatives to deliver to healthcare professionals. These would stress that: "In RELY there were numerically fewer fatal bleeds compared to warfarin."

There were concerns about the RE-LY trial early on. The trial randomised participants to either warfarin or one of two doses of dabigatran (150 mg or 110 mg twice daily) and was published in the *New England Journal of Medicine* in September 2009.[4]

The paper concluded that patients given the 150 mg dose of dabigatran had significantly lower rates of stroke or systemic embolism than those given warfarin. They also had similar rates of major bleeding.

The fact that it was the first new oral anticoagulant for over half a century, also allowed the new drug to benefit from regulatory policies promoting innovation; before being licensed it was studied in a single large phase III trial rather than in at least two trials, as is normally required for approval.[1]

Questions over data

When the data were first sent to the FDA to gain approval for the drug, the US agency had concerns over misreporting of events. The FDA issued a "Refuse to File" notice and instructed Boehringer to launch a review of the data relating to any of these missed events in early 2010.

"We recognize that there may be occasional inaccuracies in a large trial database; however, the frequency of errors in the data sets impedes our ability to perform an adequate review, and undermines our confidence in your data," a letter from the FDA to the company in February 2010 said.[5]

Two months later, in April 2010, the company refiled its drug application. Its review of the data had identified a further 3848 events in 3054 participants (out of just over 18 000 in the clinical trial) for which there was "potential data inconsistency." Of

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these cases, 425 were sent back to the original clinical sites for re-evaluation.

Overall the review found similar numbers of major bleeds in each arm of the trial and "did not materially change the results," the accompanying correction in the *NEJM* said.

But when the drug application was originally filed with the FDA and in the *NEJM* paper, there were more myocardial infarctions in the dabigatran arm than the warfarin arm—one of the only worse reported outcomes for dabigatran overall. However, when the data were reviewed at the FDA's behest, the investigators identified 32 new cases of myocardial infarction (four clinical and 28 silent) based on the new appearance of pathological Q waves on routine echocardiography that were mainly in the warfarin arm of the trial. They also found 69 new cases of major haemorrhage.

Documents released during US litigation show that in a mock question and answer session before the FDA advisory committee meeting to consider whether to approve dabigatran in valvular atrial fibrillation, one of the principal investigators, Stuart Connolly, professor of medicine at McMaster University and a cardiac electrophysiologist at Hamilton Health Sciences in Canada, said:

"In the post database lock period, we then specifically went and looked at all of the ECGs to determine whether or not there was evidence of silent myocardial infarction based on the ECGs alone.

"It's a relatively imprecise way of diagnosing myocardial infarctions in my opinion. We had approximately 450 cases where the site had reported a new Q wave to have occurred when one previously wasn't there and we evaluated those; in the end there were 28 silent myocardial infarctions documented and they were almost distributed evenly across the three groups, which was different from the clinical myocardial infarctions where there was about a 30% higher rate in dabigatran," he said.

The updated results were reported in a correction to the *NEJM* paper published in November 2010. The correction stated: "All these newly identified events were adjudicated in a blinded fashion and in accordance with the study protocol."[6] The difference in number of myocardial infarctions between dabigatran and warfarin has been dismissed as due to chance because of the small number of events.[7] Yet there were fewer intracranial haemorrhages (155) than myocardial infarctions (270) in the updated RE-LY results, raising questions as to why the difference in intracranial haemorrhage is described as a benefit rather than a chance occurrence.

Lack of blinding

However, the academics who wrote the *Therapeutics Letter* expressed concern over the effect that the design of the trial might have on the results.[2] It was open label, meaning that clinicians and trial participants knew which drug was being given. The regulators accepted this design only on the understanding that adverse events would be referred to a blinded adjudicator to assess if the event was caused by the drug or what led to an event. However, this can lead to a risk of bias. Indeed, the academics said this was "amply demonstrated" in the clinical trials of another early direct thrombin inhibitor, ximelagatran, that did not receive regulatory approval.

In an unblinded clinical trial similar to RE-LY, ximelagatran was associated with numerically fewer strokes and systemic emboli compared with warfarin, relative risk=0.71 (95% confidence interval 0.48 to 1.07).[8]

However, in a follow-up double blinded trial, there were more strokes and systemic embolisms with ximelagatran (1.38, 0.91 to 2.10).[9] All this leads to questions about the regulatory decision to licence a drug on the basis of a single open label trial when the regulators had identified serious concerns. A transcript of the FDA's advisory committee shows that the US agency found "that knowledge of treatment arm [by doctors and patients] may have led to important differences in the treatment of subjects," adding: "For example, if a subject experienced an ischemic stroke, TIA (a non-endpoint event) or minor bleed, she was more likely to have her study medication permanently discontinued in the dabigatran than the warfarin treatment arms."[10]

The FDA also had grounds to believe the adjudicator was not always blinded. Indeed, FDA documents suggest that the company knew that as many as 20% of the documents reviewed by the adjudication core committee contained text that could have potentially unblinded reviewers. A review by one of the FDA's own officials found identifying information in 17%.[10]

In the FDA expert committee transcript, there is also speculation that visits to monitor international normalised ratio (INR) for those in the warfarin group may have led to the identification of more clinical events than in the dabigatran group, who had no monitoring visits. "Dr Temple: I think you're wondering whether the INR visits might have led to more capture of events, even though those were not clinical events in the usual sense."

Litigation evidence

But as the company was revelling in the drug's success, legal cases began to emerge. In the process of this litigation, plaintiffs' lawyers pointed out that some cases of fatal bleeding did not seem to have been counted in either the original analysis or the FDA mandated review. While their deaths had been counted, their bleeds had not.

The BMJ has spoken to the families of two of the people who participated in the trial. Gary Duncan had been enrolled in the RE-LY trial when he slipped and fell on ice in Missouri in February 2007. Moments later, the 57 year old was found by his daughter slumped against a wall with blood coming from his nose and mouth. The bleeding made it impossible to give mouth to mouth resuscitation at the scene, and doctors at the local hospital failed to resuscitate him. According to the legal documents, Ms Duncan asked the attending doctors about the bleeding at the time but got no response.

Eight months later another participant in the RE-LY trial, Ken Barndt, 66,was involved in a car crash in Perkasie, Pennsylvania. Although conscious when he reached hospital, his blood pressure dropped and surgeons removed his spleen to stem internal bleeding. According to health records released as part of the legal proceedings, doctors noted that Barndt had hypovolaemic shock and coagulopathy caused by treatment with an "experimental blood thinner." They called the drug company immediately and were told that there was no antidote: fresh frozen plasma was the only possible treatment. Barndt died the following day from a cardiac arrest.

To this day, there is no antidote to dabigatran on the market—although a fully humanised antibody fragment called idarucizumab is in clinical trials. (http://clinicaltrials.gov/show/NCT02104947)

The histories of the families of the two men have been made publicly available in a US federal and state lawsuit against Boehringer. On 28 May 2014, the company announced that it had settled about 4000 cases for $650m (£380m; €480m), but

denied wrongdoing saying that it had settled the lawsuit to avoid lengthy litigation.

"From the time Pradaxa launched, Boehringer Ingelheim properly advised healthcare professionals and patients about its benefits and safety, working closely with US, European, and many other regulators to ensure healthcare professionals and patients had the information they needed," Andreas Neumann, head of the legal department and general counsel said in a statement.[11]

Although both men had major bleeds immediately before their deaths, neither was counted as having had one in the company's original submission to the regulator when applying for approval in 2009. Nor were they identified in the FDA mandated review in 2010.

In October 2013, Barndt's fatal bleed and a further six cases from the trial (n=7) were brought to the company's attention by the families' legal teams, who were characterised in company documents as "litigation adversaries."

In both Barndt and Duncan's cases the unblinded clinicians whose care they were under during the trial listed them as having died from a cardiovascular event. Documents released during US litigation, however, show that in neither case did clinicians fill in a major bleed case report form. Completion of the form, to be sent to the blinded adjudicator along with the patient's medical history, was required by the trial protocol. Both Duncan and Barndt were in the dabigatran arm of the trial.

As a result, the company "implemented targeted reviews of select data to determine whether there were any and how they were distributed" in the three arms of the RE-LY trial. "RE-LY's results would only change if there were a very large number of additional unidentified major bleeds on dabigatran and none or few on warfarin," its review document produced in May this year says.

This was the third time the number of bleeds in the RE-LY trial had been evaluated—first during the trial itself, then in the FDA mandated review, and now in a "targeted" review prompted by information uncovered by lawyers acting for the families.

This third evaluation was completed while the company was still involved in litigation. It found eight unreported fatal bleeds: three in the dabigatran 110 mg arm of the trial, two in the 150 mg arm, and three in the warfarin arm. Both the FDA and EMA are aware of the review.

A Boehringer spokesperson told *The BMJ*, "Our targeted review has not demonstrated any distribution that would change RE-LY's overall findings."

It is still not clear whether the fatal bleeds experienced by Barndt and Duncan have been counted as serious adverse events caused by the drug. When *The BMJ* asked if their bleeds had been included, a spokesperson said: "I am surprised and disappointed that you would ask these questions. As I am sure you know, clinical trial data is anonymised at patient level and it would be a serious ethical breach to talk about individual patient cases. I would hope that you would respect the anonymity that sits alongside—and is an integral part of—the clinical trial process and not name individual patients who may or may not have been involved in clinical trials for our medicine."

We also asked if the company is now confident that it has clearly identified all missed events. A spokesperson said: "We are confident in RE-LY's conclusions. While it is still possible that some events have not been identified, based on our reviews of RE-LY and the post-marketing analyses of our medicine, we are confident that any such events would be distributed evenly among treatment groups and would not affect RE-LY's findings."

But how independent and objective can such reviews be if undertaken by the company, especially if the results could affect the outcome of litigation or drug approval?

The company told *The BMJ* that the RE-LY trial "was conducted and coordinated by an independent research institute" that "oversaw the evaluation and adjudication of bleeding events and strokes."

However, it has emerged—and Boehringer Ingelheim has confirmed to *The BMJ*—that the FDA mandated review was conducted by company scientists and overseen by the company's most senior executive, Andreas Barner, who was spokesperson for the board of managing directors and responsible for research and development in medicine at the time.

Boehringer told *The BMJ* that Barner "personally did not engage in reviewing the RE-LY trial data or drawing conclusions from the review—he left that to our scientists."

But why did the regulators allow this level of involvement from senior executives when so much was at stake? And is this acceptable?

The BMJ asked Steve Nissen, department chair of cardiovascular medicine at the Cleveland Clinic and one of the members of the FDA's advisory committee considering dabigatran for use in non-valvular atrial fibrillation.

"With regard to collection of cardiovascular event data, it is imperative that ascertainment of cardiovascular events be performed by a committee completely independent of the sponsor and fully blinded with respect to the assigned treatment group. Involvement by the sponsor in the adjudication process undermines the scientific integrity of any trial and can potentially result in inaccurate conclusions. Such involvement is not acceptable," he said.

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