Timeline of events in the process of aproval and marketing of the drug Pradaxa® till July 2014 including litigatin data

	Date	Organization	Event reportetd	BMJ 001	BMJ 002	BMJ 003
	no date	BI internally	Internal documents show how the company had produced extensive analyses that show how that bleeding risk may be reduced. The company found that if the plasma level of the drug were measured and the dose was adjusted accordingly major bleeds could be reduced by 30-40% compared with well controlled warfarin. The adjustment would have little or no effect on the risk of ischaemic stroke. It has also identified the plasma levels at which the dose adjustment should occur to reduce the risk of a major bleed. The conclusion of the analyses was: “Optimally used (=titrated) dabigatran has the potential to provide patients an even better efficacy and safety profile than fixed dose dabigatran and also a better safety and efficacy profile than a matched warfarin group.”	BMJ_001 page 1, 2nd collom section 2		
	2008	BI internally	From an early stage, Boehringer planned to develop and market a drug that did not require plasma level monitoring. Internal documents show that even though there had been deaths associated with major bleeds in the clinical trial and there was no antidote—a decision had been made not to support the development of a bedside monitoring device. The rationale for this was laid bare in an email on 3 June 2010. An employee from the cardiology division of the company brought up the issue of the utility of such a device. In an email they said: “2 years ago [in 2008] there was an informed decision NOT to develop this. As this would go against the ‘no monitoring’ idea/claim.”	BMJ_001 page 5, 1st collom section 1		
	Sep 09	BI publication	RE-LY Study is published (NEJM)			
	late 2009	Concerns on RE-LY study design	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 ……		BMJ_002 page 2, 1st collom section 7; 2nd collom Section 2	
Continuation of the above			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.”		BMJ_002 page 2, 1st collom section 7; 2nd collom section 2	
	Feb 10	FDA	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		BMJ_002 page 1, 2nd collom, section 6-7	

	Apr 10	BI	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 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.		BMJ_002 page 1, 2nd collom Section 8; 3rd page section 1-3	
	Apr 10	Qoute from the litigation on Dabigratan	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.		X BMJ_002 3rd page 1st collom section 4-6	
	2010	FDA	At every stage in dabigatran's evaluation, licensing, and marketing, the claim that there was no need to monitor drug levels has been central. It has been a factor in the cost benefit evaluations by bodies like NICE and the successful marketing and widespread uptake of the drug. It was even highlighted in an FDA press statement in 2010 at the time of its US approval: "Unlike warfarin, which requires patients to undergo periodic monitoring with blood tests, such monitoring is not necessary for Pradaxa [dabigatran]," said Norman Stockbridge, director of the division of cardiovascular and renal products in the FDA's Center for Drug Evaluation and Research.7	BMJ_001 page 2, 1st collom section 6-8		
	2010	FDA	During the US drug approval process in September 2010 one FDA adviser also raised the question of monitoring dabigatran because of the large differences in plasma levels among people taking the drug. "I'm struck by what my eyeball tells me about a five-fold variability [in plasma levels] within the 90% 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 in 2010. However, McGuire's concerns were not pursued by the agency.	BMJ_001 page 2, 2nd collom section 4-5		
	Oct. 2010	FDA	Aproval for use for prevention of stroke in patients with artherial fibrialation			
	2010	EMA	Documents from early 2010 show that BI identified The 200 ng/mL concentration is the value at trough not to be exceeded because of the increased risk of bleeding.This value is reiterated in EMA's published drug assessment report. It also stipulates a lower end of the range of 48 ng/mL	BMJ_001 page 2, 2nd collom section 3-4		
	early 2011	Canddian 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]		X BMJ_002 page 1, 1st collom Section 6	
	Aug 11	EMA	Aproval for use for prevention of stroke in patients with artherial fibrialation			

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	Aug 11	BI internally	Internal documents circulated within the company in August 2011 show that employees completed a subgroup analysis of these data. …. The paper, which was first drafted in August 2011, examined a critical question: how much did the benefits (reduced risk of ischaemic stroke) and harms (increased risk of bleeding) vary across the drug's plasma concentration range. This "has mportant implications for the benefit-risk ratio in individual patients," both the draft and published papers said. They found that there was a fivefold variation in blood plasma concentration with each dose. Reilly's paper reported that renal function was the most important determinant of dabigatran concentration, and age is the most important covariate. "The large majority of patients achieve a favourable balance of benefit and risk with a fixed dose of DE [dabigatran] 110 or DE [dabigatran] 150, guided by a consideration of patient characteristics," the published paper said. However, the 2011 draft also suggested there was an optimal plasma concentration range of the drug and went beyond tailoring dose according to patient characteristics. It found that there was a fivefold variation in blood plasm	BMJ_001 page 3, 1st collom section 8; 2nd collom 2 4		
Continuation of the above			However, the 2011 draft also suggested there was an optimal plasma concentration range of the drug and went beyond tailoring dose according to patient characteristics. It found that there was a fivefold variation in blood plasma concentration with each dose. "Monitoring of plasma oncentration or antithrombotic activity . . . would be required to identify these patients. A dose adjustment could improve the benefit-risk ratio," according to the 2011 draft seen by The BMJ.	BMJ_001 page 3, 2nd collom section 4		
	2011	EMA	During discussions about licensing the drug for non-valvular atrial fibrillation, the EMA was concerned that dabigatran would be "largely used in an elderly population which is known to be at a higher risk of bleeding"	BMJ_001 page 3, 1st collom section 3		
	2011	BI/EMA	EMA was concerned that dabigatran would be "largely used in an elderly population which is known to be at a higher risk of bleeding" —a concern that internal company documents show to be justified. Boehringer Ingelheim marketing data showed that "45% of Pradaxa patients are 76 years or older" and "30% of patients are 80 years or older." However, only 40% of participants in the RE-LY trial were over 75 and 17% over 80.	BMJ_001 page 3, 1st collom section 4		
	end of 2011	FDA	By the end of 2011 regulators were concerned as postmarket reports accumulated about cases of severe bleeding and deaths among patients taking dabigatran. A *QuarterWatch* report analysed all the adverse events submitted to the FDA's reporting system in 2011.[14] It found the most commonly identified drugs reported to the FDA were the anticoagulants dabigatran and warfarin. For dabigatran alone, this included 542 patient deaths and 2367 reports of haemorrhage. Warfarin accounted for 72 deaths in the same period.	BMJ_001 page 3, 1st collom section 5		
	Dec 2011	BI/EMA	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,16 and the EMA asked the manufacturer for a detailed tabulation of all reported deaths from bleeding. The EMA assessment,17 a company internal study,18 and an independent outside review19 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.			BMJ_003 Page 3, 2nd collom, section 1-2
	Dec 2011	BI/EMA continuation of the above	Why were so many dabigatran bleeds being reported? Data now publicly available on plasma concentration of dabigatran in RE-LY participants provides one answer.[6] At least 10% of patients had peak plasma level concentrations ≥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.[20] Other factors could increase bleeding risk further. The EMA concluded that concomitant therapy with antiplatelet agents such as aspirin or clopidogrel roughly doubled bleeding isk with either dabigatran or warfarin.[13] And the 12% stronger eformulation that was being prescribed by doctors increased the risk of bleeding beyond the rates reported in the RE-LY sub-study.			BMJ_003 Page 3, 2nd collom, section 3

	early 2012	EMA	As the number of fatal bleeds accumulated and company employees deliberated Reilly's analyses, the EMA started to formally consider the key issue that the manufacturer was trying to avoid: that dabigatran would need to be monitored and the dose adjusted. In early 2012 the agency convened its scientific advisory group of experts to give it advice about these issues. Specifically, it wanted to know if there was a "need for stronger and more specific recommendations for measurement of dabigatran related anticoagulation," specifically in those groups at increased risk of bleeding. The European agency also asked the committee to "discuss and suggest appropriate monitoring frequency and laboratory tests."	BMJ_001 page 4, 1st collom section 4		
	March 2012	BI/EMA	On 9 March, 2012, Boehringer gave a presentation to the committee, details of which The BMJ has obtained under a freedom of information request, along with the agency's minutes of the meeting. The EMA's minutes show that routine monitoring of anticoagulant activity was discussed "in depth" by the committee. However, most experts voted against it. The committee thought that this was justified because "the desired plasma drug level and the therapeutic window are not known" and "there is significant variability of more widely available tests such as the aPTT [activated partial thromboplastin time] making interpretation difficult." In the end, the final recommendations simply stressed the need to monitor renal function and patient characteristics before and during treatment and "make dose reductions in certain patients"—and not routinely measure plasma concentrations or anticoagulant activity. Dabigatran is predominantly excreted by the kidneys. Some of the analyses and conclusions outlined in Reilly's 2011 paper, which was produced over six months before EMA's safety meeting in March 2012, were absent from the company's presentation to the committee.	BMJ_001 page 4, 1st collom section 6-12; page 4 2nd collom section 1		
Continuation of the above			company's presentation include a graph showing that beyond a certain plasma concentration of the drug major bleeding events continued to increase as the plasma levels increased with little effect on rates of stroke and systemic embolism.12 This graph was, however, published in 2013 in the Journal of the American College of Cardiology. Also absent from the presentation were data showing that some people taking dabigatran may have a suboptimal dose, putting them at "an appreciably higher" stroke risk. In the meeting, company officials highlighted the importance of measuring creatinine clearance to assess renal function. The company also chose to present statistics in which the plasma level variability seemed to be about 2.3-fold instead of 5.5-fold as documented in Reilly's paper. The presentation added that the European label currently includes monitoring for renal function and cut-off values for dabigatran exposures with increased bleeding risk and plasma level data from RE-LY. But stated: "Routine monitoring of the anticoagulant activity is not necessary."	BMJ_001 page 4, 1st collom section 6-12; page 4 2nd collom section 1		
	March 2012	EMA	The EMA, on the other hand, considered whether to require plasma level testing for dabigatran.17 The EMA had already obtained a therapeutic range from Boehringer Ingelheim, 48-200 ng/mL, which was included in the EU approved product ANALYSIS 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.25 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.26 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			BMJ_003 Page 3, 2nd collom, section 5; Page 4, 1st collom, section 1-2
Continuation of the above			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."			
	Apr 12	BI	Once on the market, dabigatran proved a rapid success. By April 2012, it had achieved blockbuster status (where annual global turnover for a medicine exceeds $1bn), prompting Boehringer board member Hubertus von Baumbach to say: "The launch of Pradaxa [dabigatran] is among the most successful market introductions in the pharmaceutical industry in the past few years."	BMJ_001 page 3, 1st collom section 1		

	June 2012	External publication British Journal of Clinical Pharmacology	In June 2012, he and a group of other academics published a paper in the *British Journal of Clinical Pharmacology* that caught the eye of company executives. It stated that testing in clinical practice has been "largely downplayed." The paper pointed out that the UK guidelines from Boehringer advocating renal testing in some patients did not go far enough, "leaving some individuals likely to be overdosed and some perhaps underdosed." It advocated the use of the Hemoclot test. Internally, the paper triggered discussions. One employee was worried about the adverse effects of dabigatran—particularly in older people. "We should not ignore that in those over 80 years old, even the 110 mg had a unfavourable trend compared to warfarin (major bleeding 80 years: hazard ratio 1.12 (95% confidence interval 0.84, 1.49)," the employee wrote, arguing that Boehringer needed to study this further before another independent group did.	BMJ_001 page 5, 2nd collom section 9; page 5 1st collom section 1-2		
Continuation of the above			The unpublished version of the Reilly paper, however, stated that "targeting a specific concentration range may optimize the benefit-risk . . . A dose adjustment could improve benefit-risk ratio," it said. But the company's presentation to the EMA's ad-hoc committee did not include this information.	BMJ_001 page 5, 2nd collom section 9; page 5 1st collom section 1-2		
→	July 2012	BI internally	However, the scientists' concern conflicted with that of some in the company. An email in October 2012 shows a company official saying that "The publication will [do] more harm that be useful for us, neither in the market but especially harmful in the discussions in the regulatory bodies."	BMJ_001 page 3, 2nd collom section 4		
	July 2012	BI internally	When discussing how best to publish analyses of data from the RE-LY trial, Stuart Connolly, one of the principal investigators of the RE-LY trial, said in an email in July 2012: "There is very good reason to never go above 200 ng/ml. It is less clear at the low end due to the paucity of events but somewhere around 40-50 seems prudent for a lower boundary."	BMJ_001 page 2, 2nd collom section 8		
	July 2012	BI internally	The company knew what damage the paper might do—and yet emails show that in July 2012 Connolly thought that it was a good paper that "will have an impact on thinking about dabigatran" and points to "optimization of safety and efficacy in the range from 40-200 ng/mL."	X		
	Spring 2013	BI internally	Soon after Boehringer told the EMA's committee that adjusting dose for plasma levels was not necessary, it was considering relaunching the drug based on adjusting the dose to a specific therapeutic range. The company wanted to know if it could find a "unique selling" point for dabigatran since rivaroxaban and apixaban—two other new oral anticoagulants—had come onto the market. "Could individualised dosing be a unique selling point for Pradaxa in the marketplace," a June 2012 document entitled "Potential mid to long term strategy for Pradaxa in SPAF [stroke prevention in atrial fibrillation]" said. The document noted that prescribers often wanted to know the extent of the anticoagulation each patient is receiving with their current anticoagulant. Company employees produced yet more analyses, which they summed up in the strategy document and accompanying slide presentation circulated to Boehringer executives. It analysed whether "a one-time initial measurement (perhaps repeated annually and in some instances, such as moderate renal impairment, in shorter intervals)" followed by titration of dabigitran to reach an optimal dose would be the	BMJ_001 page 5, 1st collom section 3-6		
Continuation of the above			After an "intense effort" using data simulations and data from RE-LY, it found that by doing this, it "could preserve the effect on ischemic stroke prevention but with a reduction of major bleeding events compared to well controlled warfarin of perhaps up to 30-40%." The data also suggested that such an approach would even lead to fewer gastrointestinal bleeds with dabigatran "compared to warfarin in such a setting."	BMJ_001 page 5, 1st collom section 3-6		

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	Spring 2013	BI / FDA	The company were also keen to get the 110 mg twice daily dose on the market in the US, and this would be needed for individualised dosing.12 “[The] FDA has indicated that such modeling data, together with clinical data (eg, a PK/PD [pharmacokinetic/pharmacodynamic] study) on a titration strategy, may be the only way forward to an approval of the 110 mg dose in the US,” the document said. After considering regulatory and other obstacles, the company has thus far not elected to pursue this strategy.	BMJ_001 page 5, 1st collom section 7-8; page 5, 2nd collom section 1		
	Feb 13	BI internally	Clemens also wrote that he believed that the findings were important and should be published but with revision. “The world is crying for this information—but the tricky part is that we have to tailor the messages smart.” Emails from February 2013 show that company employee Jutta Heinrich-Nols wrote to other employees to recommend that the company reconsider whether to publish this study. “This will make any defense of no monitoring to HA [health authorities] extremely difficult (i.e. Health Canada, TGA) and undermine our efforts to compete with other NOACs [new oral anticoagulants]. As I am not empowered to release or stop any publications I would like to ask you to check once again whether this is really wanted.,” an email said. Publishing the research results, she warned, could make it “extremely difficult” for the company to defend its long-held position to regulators that dabigatran did not require monitoring.	BMJ_001 page 3, 2nd collom section 8-9		
	2013	BMJ	The BMJ contacted the three independent doctors working with the data and asked them about the apparent conflict around what was contained in the paper. Wallentin said that while the academics had access to the RE-LY database and freedom to analyse what they wanted, “all scientific projects are submitted to and approved by the RE-LY publications committee. The content of all publications are of course at the end based on discussions followed by modifications to reach a consensus among all coauthors,” he said. The BMJ has found that the company did defend the notion that the drug did not require monitoring of plasma levels or anticoagulant activity to health authorities.	BMJ_001 page 4, 1st collom section 2-4		
	Sep 13	BI publication	Official yet incomplete publication of the internal paper from 2011 Some of the conclusions of this analysis were eventually published online in the Journal of the American College of Cardiology in September 2013 under the title “The effect of dabigatran plasma concentrations and patient characteristics on the frequency of ischemic stroke and major bleeding in atrial fibrillation patients.” The lead author was Paul Reilly, a Boehringer employee, and coauthors included other company employees as well as Stuart Connolly and Salim Yusef from McMaster University in Canada and Lars Wallentin from the Uppsala Clinical Research Centre, Sweden.	BMJ_001 page 3, 1st collom section 9		
	Sep 13	BI publication, continuation of the above	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.6 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 variably. 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.			BMJ_003 Page 2, 1st collom, section 2-3
Continuation of the above			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). As a result, a small difference in metabolic activation or kidney function could have a large effect on plasma level and bleeding risk.			BMJ_003 Page 2, 1st collom, section 2-3

	March 2014	US litigation against BI	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. ….. Gary Duncan had been enrolled in the RE-LY trial when he slipped and fell on ice in Missouri in February 2007. (comment by author: Mr. Duncan tied on fatal bleed on the same day) …. Ken Barndt, 66,was involved in a car crash in Perkasie, Pennsylvania. (comment by author: Mr. Barndt tied on fatal bleed on the same day)		X BMJ_002 page 2_ 2nd colom section 3 / page 3 1st collom section 3-5	
Continuation of the above			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.		X BMJ_002 page 2_ 2nd colom section 3 / page 3 1st collom section 3-5	
	March 2014	BI	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.		X BMJ_002 P1_ 1st colom section 2 - 3	
	2014	Evidence from several sources	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."27 The published sub-study of RE-LY concluded, "Individual benefit-risk might be improved by tailoring dabigatran dose."6 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.28 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.17			BMJ_003 Page 4, 1st collom, section 3-4
Continuation of the above			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.			