dtbn
DRUG AND THERAPEUTICS BULLETIN OF NAVARRE, SPAIN
YEAR 2016
VOL 24, No 1
www.dtb.navarra.es
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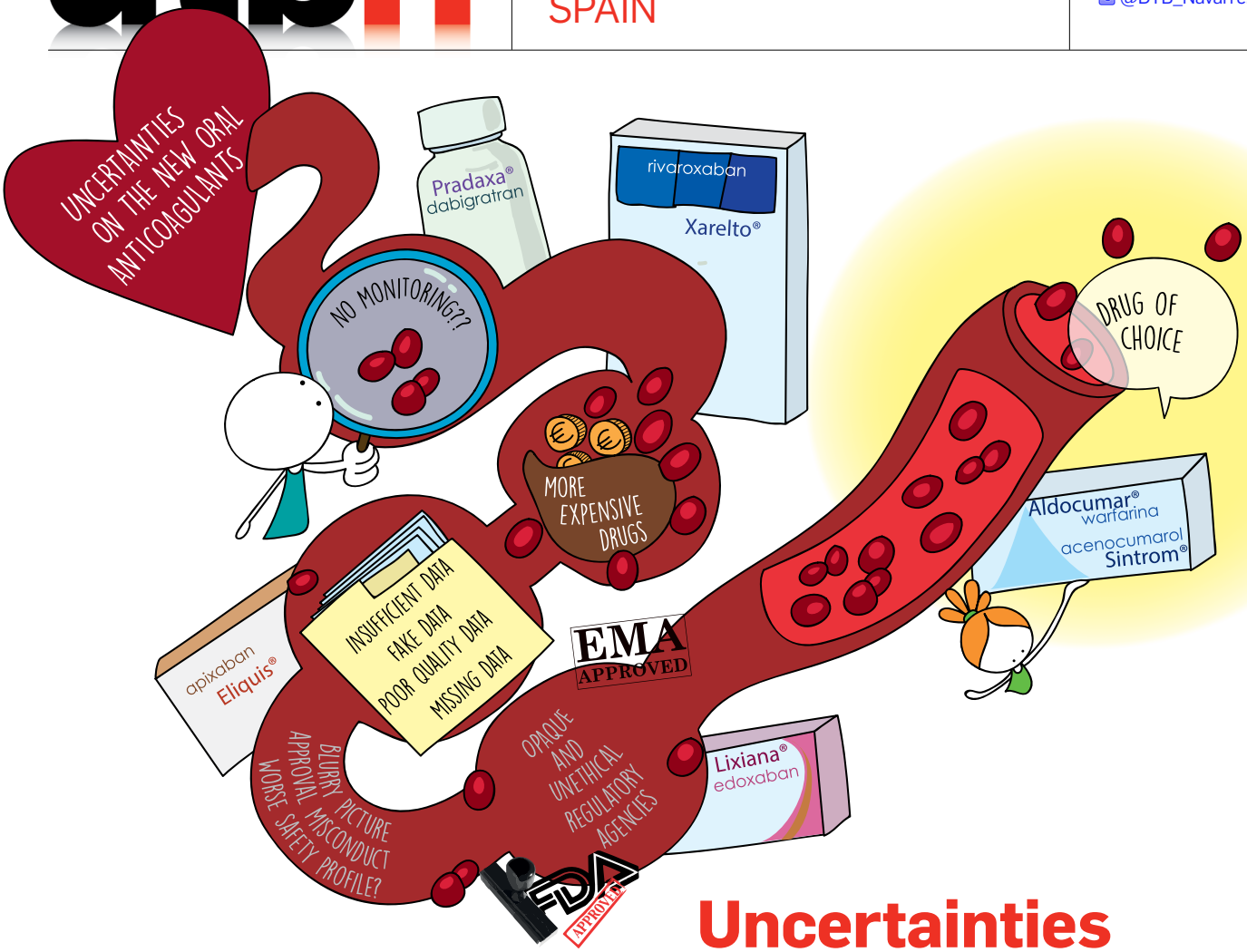

Uncertainties about new oral anticoagulants in atrial fibrillation

Deficiencies and irregularities in the authorization process

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abstract

Objective: To list the irregularities recently identified in the pivot clinical trials that led to the approval of a number of new oral anticoagulants for patients with atrial fibrillation. **Methods:** A search was made on PubMed (last updated on 31/12/2015) for the new evidence published that led to the approval of dabigatran, rivaroxaban, apixaban and edoxaban. **Results and conclusions:** The FDA decisions to approve the use of dabigatran, rivaroxaban, apixaban and edoxaban for atrial fibrillation were based on pivotal clinical trials that were performed with numerous irregularities including the deliberate omission and fabrication of data. By approving the use of these drugs, regulatory agencies showed a worrying lack of rigor, since they ignored the serious deficiencies detected by their own inspectors in pivotal trials. No reliable information is available on the harm/benefit ratio of dabigatran, rivaroxaban, apixaban and edoxaban for atrial fibrillation vs. warfarin. Regulatory agencies should make complete data from trials publicly available, to ensure transparency and provide reliable information. This would allow for the optimization of treatments. **Keywords:** Dabigatran, rivaroxaban, apixaban, edoxaban, atrial fibrillation.

Introduction

Vitamin K antagonists are the anticoagulators of choice for patients with atrial fibrillation. The purpose of these drugs is to reduce the risk of thromboembolism in this type of patients. Warfarin is the most widely used oral anticoagulant worldwide, whereas the use of acenocumarol is more widespread in Spain.

The problem with these therapies is that they require regular monitoring of Prothrombin Time (PT), which is measured using a blood test called International Normalized Ratio (INR). Although this method is not convenient for patients, it guarantees that anticoagulation levels are appropriate and allows dose adjustment such as when interactions with other drugs or foods occur.

New oral anticoagulants based on different mechanisms of action have been approved for use. Theoretically, the advantage of these new agents is that they have an anticoagulant effect similar to that of Vitamin K antagonists, but they do not require regular monitoring of anticoagulation levels.

In March 2008, dabigatran, a direct thrombin inhibitor was approved in Europe. Initially, it was indicated for the prevention of venous thromboembolism in patients undergoing hip or knee replacement surgery. Subsequently, dabigatran was approved for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation plus one of the following risk factors:

- Previous stroke, transient ischemic attack or systemic embolism;
- A left ventricular ejection fraction of less than 40%;
- Symptomatic heart failure (NYHA ≥ 2);
- Age ≥ 75 years;
- Age ≥ 65 years plus diabetes mellitus, hypertension, or coronary artery disease.

A few months later, in September 2008, the European Medicines Agency (EMA) approved the use of rivaroxaban, an orally active direct factor X inhibitor for the prevention of venous thromboembolism in patients undergoing hip or knee replacement surgery. Rivaroxaban was also approved for the prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation plus one or more risk factors including: congestive heart failure, hypertension, age ≥ 75 years, pre-existing diabetes mellitus, previous stroke or transient ischemic attack.

In May 2011, the EMA approved the use of apixaban, another orally active direct factor X inhibitor with the same indications as rivaroxaban.

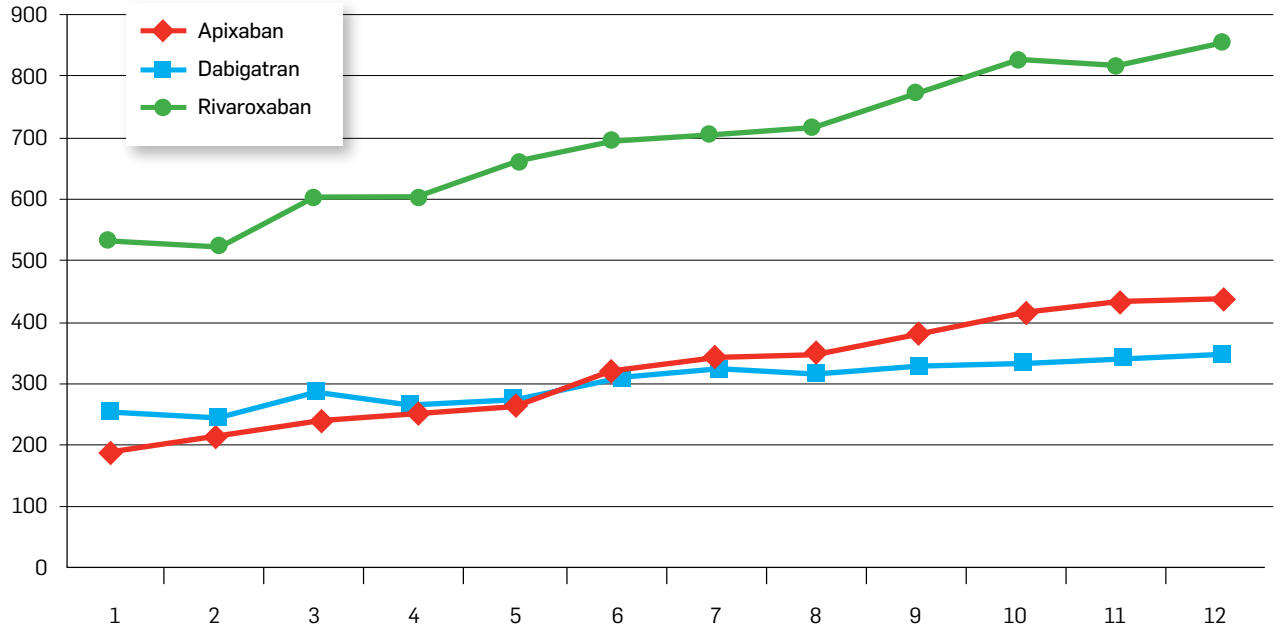
Finally, in June 2015, the EMA approved the use of edoxaban –the third orally active direct factor X inhibitor– with the same indications as the other two inhibitors.

The Spanish Medicines Agency published a report in collaboration with the Autonomous Communities on the therapeutic positioning of new oral anticoagulants.[1]

By December 2015, a total of 10,043 patients were receiving anticoagulation therapy in the province of Navarra, Spain (650,000 population). Most patients took acenocumarol (82.1%), whereas the remaining patients took rivaroxaban (8.5%), apixaban (4.4%), dabigatran (3.4%) or warfarin (1.6%).

Between January and December 2015, the proportion of patients taking new anticoagulants rose from 10.5% to 16.3%, which accounts for a 5.8% increase in absolute terms (figure 1).

Figure 1. Evolution of the number of patients taking new oral anticoagulants in Navarre, Spain, in 2015.



The new anticoagulants were approved based on the results of a series of phase III trials assessing the effects of these new agents vs. warfarin.[2,3,4,5] A number of reports have recently been published reviewing the validity of the process of development and testing of dabigatran, rivaroxaban, apixaban and edoxaban. The concerning results obtained raise doubts about the risk-benefit of these drugs as anticoagulants.

The objective of this paper is to list the irregularities recently identified in the pivotal clinical trials that led to the approval of a number of new oral anticoagulants for patients with atrial fibrillation.

Methods

A search was made on PubMed, FDA, EMA and Drug Bulletins from the *International Society of Drug Bulletins* (last updated on 31/12/2015) for the new evidence published that led to the approval of dabigatran, rivaroxaban, apixaban and edoxaban.

Uncertainties about dabigatran

Need for regular monitoring of anticoagulation in patients receiving dabigatran[6]

The approval of dabigatran was based on the data provided by an open "non-inferiority" trial with dabigatran versus warfarin known as the RE-LY trial.[2] The FDA and the EMA adopted opposing positions and provided different guidelines for the use of the data provided by this trial. The FDA did not initially approve the use of this drug due to the numerous deficiencies found regarding the quality of the data provided by the company. Finally, the drug was approved, but only at a dose of 150 mg/12h on the grounds that the 110 mg/12h dose is less effective for the prevention of stroke and disability. On its part, the EMA was more concerned about the hemorrhages that the drug could cause but approved both the 110 mg/12h and the 150 mg/12h doses.

The RE-LY trial, published in 2009, involved a total of 18,113 patients. It included a subgroup of 9,183 patients who underwent monitoring of drug concentrations in plasma. The company, however, did not disclose this information, which was finally revealed by court order in 2013 after a legal procedure in the USA. After a month on 150 mg/12h, maximum drug concentrations ranged between 2.3 and 1,000 ng/ml.

In a meeting held with the EMA, the company stated that it was not necessary to monitor plasma drug concentrations, since variability was only 2.3-fold. Subsequently, EMA technicians detected errors in the data analysis performed by the company. From a conservative perspective, if 20%

of patients at the upper and lower limit of the distribution curve were removed, plasma concentrations were 5.5-fold higher in the patients with the highest concentrations of dabigatran as compared to patients with the lowest concentrations.

The probability that a patient had an hemorrhage increased from 2-3% at concentrations of 50 ng/ml to 9% at concentrations close to 300 ng/ml and to more than 12% at higher concentrations.

To solve this problem, the company proposed the FDA to approve the 110 mg/12h dose and contraindicate the use of dabigatran in patients with severe renal failure. Yet, the company never suggested the need to monitor drug concentrations in plasma.

According to a reanalysis of the RE-LY trial performed by a group of investigators in Japan,[7] the safe use of dabigatran is seriously compromised if drug concentrations in plasma are not monitored.

Excessive variability in plasma concentrations might reduce drug effectiveness in preventing thromboembolism if the patient receives a subtherapeutic dose, and increase the risk of hemorrhage if the dose administered is too high. In the RE-LY trial, the incidence of major and minor bleeding was 16.4%/year in patients that took high doses of dabigatran (150 mg/12h) *vs.* 18.1%/year in the group taking warfarin, RR=0.91 (0.86-0.97).

Uncertain Data

Apparently, bleeding is less frequent with dabigatran than with warfarin.[8,9] However, there is evidence challenging the authenticity of the data provided by the RE-LY trial. The EMA requested that the company perform a reanalysis of the data. Yet, the incidence of fatal and life-threatening bleeding in the trial is still unknown.[8] The dropout rate reported by the company was 21% for the patients taking dabigatran vs. 17% for the patients on warfarin. Nevertheless, the total number of severe adverse events was never disclosed. Although some authors asked the company to provide this information, the company refused to reveal it. Therefore, the net benefit of dabigatran is unknown.[9]

In accordance with internal company documents,[10,11] the incidence of bleeding could be reduced by 30-40% if drug concentrations in plasma were monitored. Dabigatran was approved in the USA in 2010. The FDA published the adverse reactions reported for this drug in 2010 including 542 deaths and 2,367 bleeding events associated with dabigatran. In contrast, 72 deaths associated with the use of warfarin were reported in 2010. Considering that warfarin is much more widely used than dabigatran, the incidence of bleeding in patients taking dabigatran in clinical practice is substantially higher as compared to that reported by the RE-LY trial. Notwithstanding the foregoing, it should also be taken into account that adverse reactions are reported more frequently for new medicines than for standard medicines.

In a meta-analysis based on the data reported by the RE-LY trial and other three trials comparing dabigatran and warfarin for patients with conditions other than atrial fibrillation, gastrointestinal tract bleeding was about 40% more frequent in the group receiving dabigatran RR= 1.41 (95% CI, 1.28-1.55).[12]

The antidote for dabigatran

Unlike warfarin –which can be antagonized with vitamin K–, when dabigatran hit the market, no reversal agent was available. The EMA recently approved the use of idarucizumab for the reversal of dabigatran's anticoagulant effect.

When idarucizumab was approved as a reversal agent, the data provided by the REVERSE-AD study had been collected from an interim analysis of data from 123 patients recruited as of April 1, 2015. The REVERSE-AD is a non-controlled study involving patients with uncontrolled bleeding who received the reversal agent. Complete reversal of the anticoagulant effects of dabigatran was achieved in more than 89% of patients. However, it should be noted that 26 patients (21.1%) died despite the use of idarucizumab.

Further doubts about the data provided by the RE-LY trial

When the company submitted the data on dabigatran for FDA approval, the reviewers expressed concerns that adverse drug reactions could have been underreported[13]. Additionally, they stated that the "considerable amount of errors in the data set prevents the realization of an adequate review".[13] Two months later, the company submitted a new data set from the trial including 3,848 additional adverse events that had not been reported previously and experienced by 3,054 patients from a total of 18,000. Of the 3,054 new cases reported, the company was asked to re-evaluate 425. Once re-evaluation was completed by the study investigators upon request of the FDA, the company reported 32 new cases of myocardial infarction and 69 new cases of major bleeding.[9]

Cardiac effects of dabigatran

Effects on patients with mechanical heart valves

The RE-ALIGN trial assessed the efficacy of dabigatran vs warfarin in patients with mechanical heart valves.[14] The trial was prematurely stopped due to a significant increase in the incidence of stroke, myocardial infarction, thromboembolic events and bleeding in the dabigatran group following heart valve surgery.

In light of the results of this trial, dabigatran is expressly contraindicated in patients with mechanical heart valves.

Dabigatran and myocardial infarction

The RE-LY trial reports that the incidence of myocardial infarction was higher in the dabigatran group than in the warfarin group, and differences reached statistical significance in the group receiving the 150 mg/12h dose.

As mentioned above, after data from the RE-LY trial had been published, the FDA asked the company to review the data set. As a result, 32 new cases of myocardial infarction were reported. Once the trial was completed, professor Stuart Connolly, one of the investigators involved in the trial, reviewed all ECG scans to identify potential silent infarctions that should have been included in the data set. In total 28 new cases were identified. Theoretically, the investigators were blinded to the groups where infarctions occurred, but Connolly reported that "silent infarctions were equally distributed across the three groups", which was not consistent with the incidence of infarctions previously reported, which was 30% higher in the dabigatran group.[8]

The higher incidence of infarction in the dabigatran group was underestimated on the grounds that, in absolute terms, the number of infarctions was low and that, following re-evaluation (when new silent infarctions were included in the data set), no statistically significant differences would be observed between dabigatran and warfarin (table 1).[15]

In contrast, the meta-analyses performed on the RE-LY trial and other trials comparing dabigatran and warfarin for other conditions[16,17] have reported a statistically significant increase of about 0.4% in absolute terms in the incidence of myocardial infarction (1.20% vs. 0.78%, OR = 1.34 (1.08-1.65). In accordance with the results of another meta-analysis, the risk of infarction also increases with the use of other thrombin inhibitors such as ximelagatran (withdrawn before commercialization) or AZD0837; therefore, it could be a class effect.

In clinical practice, treatments are temporarily or permanently being changed from warfarin to dabigatran for cardioversion.[18] In a post-hoc analysis of data from the RE-LY trial, no differences were found between warfarin and dabigatran related to the incidence of thromboembolism or bleeding in patients with atrial fibrillation undergoing cardioversion.

Observational studies with dabigatran

The FDA performed an observational pharmacovigilance study and concluded that the safety profile of dabigatran is similar to that of warfarin regarding the risk of bleeding.[19] Yet, this study was performed using a new pharmacovigilance method in pilot phase (Mini-Sentinel) that has serious limitations regarding the quality of data and possibility of performing data analysis, since the amount of clinical data collected was inadequate. These results are inconsistent with those obtained in one of the meta-analyses mentioned above, which reported a 40% increase in the incidence of bleeding with dabigatran.[12]

Another study[20] was based on data from the USA MEDICARE database in 37,587 patients/follow-up year. It concluded that the use of dabigatran increased the risk of ischemic stroke, intracraneal hemorrhage and death and reduced the risk of gastrointestinal hemorrhage in older patients with atrial fibrillation. However, given that cases of stroke, hemorrhage and death were not validated in this study, the results obtained should be interpreted with caution. Failure to validate these conditions was justified by the authors by the fact that other USA databases had already been validated for these conditions. But such databases are not similar to MEDICARE and they were validated between 2002 and 2008 using a small sample size that was inadequate for validation (about 200 clinical records for each condition).

Based on the MEDICARE database, another study concluded that dabigatran increased the risk of hemorrhage as compared to warfarin: HR = 1.30 (IC95% 1.20-1.41) for all-cause bleeding; HR = 1.58 (IC95% 1.36-1.83) for major bleeding, and 1.85 (IC95% 1.64-2.07) for gastrointestinal

Table 1. Incidence of myocardial infarction in the RE-LY trial before and after data re-evaluation.

	Dabigatran 110 mg (n=6,015)		Dabigatran 150 mg (n=6,076)		Warfarin		Dabigatran 110 mg *vs* warfarin		Dabigatran 150 mg *vs* warfarin	
	No.	%/year	No.	%/year	No.	%/year	RR (IC95%)	p	RR (IC95%)	p
BEFORE[2]	86	0,72	89	0,74	63	0,53	1,35 (0,98-1,87)	0,07	1,38 (1,00-1,91)	0,048
AFTER[16]	98	0,82	97	0,81	75	0,64	1,29 (0,96-1,75)	0,09	1,27 (0,94-1,71)	0,12

bleeding. In contrast, the risk of intracraneal bleeding was higher with warfarin, HR = 0.32 (IC95% 0.20-0.50).[21]

The use of dabigatran was associated with a higher incidence of major bleeding (regardless of the site), a higher risk of gastrointestinal bleeding and a lower risk of intracraneal hemorrhage. Therefore, dabigatran should be prescribed with caution, especially in the case of high-risk patients.

Denmark has built an appropriately validated database of the clinical records of the whole population of the country.[22] At least three observational studies with dabigatran based on this database have been published. In the first study, the authors found no differences in the incidence of thromboembolism and hemorrhage between the patients who initiated a treatment with dabigatran or with warfarin. Conversely, the incidence of thromboembolism and hemorrhage increased in the patients who changed from long-term warfarin therapy to dabigatran, as compared to warfarin.

The same authors published a study involving only patients starting anticoagulant therapy and obtained results similar to those of a previous study.[23] Thus, no differences were found related to the incidence of thromboembolic or bleeding events between the warfarin and the dabigatran group in patients not previously treated with oral anticoagulants.

Another study based on the Danish database was performed with patients who either changed from warfarin to dabigatran (n= 3379) or continued with warfarin (n= 49.868)[24]. The authors observed a higher risk of infarction within the first 60 days on treatment in the patients who changed from warfarin to dabigatran (dabigatran 110 mg, HR= 3.01; 1.48 to 6.10; dabigatran 150 mg, HR=2.97; 1.31 a 6.73). The conclusion was that the risk of infarction increased within the first days when patients changed from warfarin to dabigatran.[24]

An observational study based on population databases from EU countries is to be conducted to assess the incidence of bleeding associated with the use of new oral anticoagulant agents.

In sum, the observational studies published so far do not shed light on the efficacy and safety of dabigatran *vs.* warfarin.

Summary on the use of dabigatran

Dabigatran was marketed with the claim that it did not require monitoring drug concentrations in plasma. However, there is no strong evidence supporting such a claim, and monitoring might be necessary. At present, there is growing concern that the incidence of hemorrhage could increase among patients taking dabigatran vs. warfarin. The use of a fixed-dose of dabigatran might lead to the administration of subtherapeutic or supratherapeutic doses, especially in older patients with unstable renal function.[25] Additionally, an increase in the risk of myocardial infarction associated with the use of dabigatran remains a distinct possibility.

Concerns about rivaroxaban

Has the non-inferiority of rivaroxaban *vs.* warfarin been sufficiently demonstrated?

Approval of rivaroxaban for atrial fibrillation was based on data provided by the ROCKET-AF study.[3] It was a non-inferiority, randomized, double-blind study comparing rivaroxaban 20 mg/d (15 mg/d with a glomerular filtration rate ranging from 30 to 49 ml/min) and warfarin at adequate doses to reach an INR between 2 and 3. A total of 14,264 patients with non-valvular atrial fibrillation aged between 65 and 78 years (mean = 73) were included in the study. The authors concluded that in patients with atrial fibrillation, rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism. There was no significant between-group difference in the risk of major bleeding.

The reviewers made two important objections to the ROCKET-AF trial.[26] The first objection was that the INR values reached in the warfarin group were worse as compared to those reached in other similar trials. Specifically, the Time-in-Therapeutic Range (TTR) was 55%. The Health Service of Navarra has analyzed TTR values in monitored patients on ambulatory care receiving anticoagulant therapy with acenocumarol. The TTR value in the last follow-up visit in 2015 was considered for analysis, and the mean TTR in the last six months was calculated. The overall TTR was 64.2%. The poor control on the warfarin group in the ROCKET-AF trial is unacceptable, considering that the patients on warfarin were monitored more closely than the patients controlled by ambulatory care who were not taking part in any trial.

The FDA reviewers declared that *the poor warfarin control, as evidenced by the overall TTR in ROCKET of 55%, biased the study in favor of rivaroxaban. The study results do not convincingly demonstrate the non-inferiority, much less the superiority, of rivaroxaban to warfarin when the latter is used skillfully*.

It has been recently revealed that there was a calibration error in the software program installed in many of the devices used in the ROCKET-AF trial for measuring INR in patients on warfarin. Miscalibration resulted in a lower reading than the actual data. As many as 18,924 complaints were received about the malfunctioning of the measuring tools, including 14 severe cases. These measurement errors resulted in the overdosing of patients on warfarin and the associated unnecessary increase in the risk of bleeding. Thus, as compared to warfarin, the risk of bleeding is probably higher with rivaroxaban than that reported by the ROCKET-AF trial.[27]

The authors of the trial performed a comparative analysis of the clinical outcomes of the patients who used the miscalibrated devices against which complaints had been made and the patients who used devices that had not been questioned.[28] Similar outcomes were observed in the two groups, which means that the type of device did not affect the results of the study. Upon request of the European Medicines Agency (EMA), the company performed a data reanalysis. Some of the INR values measured using the miscalibrated devices were compared to those measured at the central laboratory using the same sample at weeks 12 and 24. It was observed that 34% of the INR values (1961/5766) measured using the miscalibrated devices were lower than those obtained in the central laboratory, and only 4% were higher. The EMA reported that these measurement errors could lead to the administration of supratherapeutic doses of warfarin.

Additionally, the company submitted three sensitivity analyses of data obtained in the trial and concluded that the clinical effects of inadequate dosage were not relevant. The EMA considered this explanation acceptable. Yet the methodology used in sensitivity tests had some limitations.[29]

Further, in research conducted by the British Medical Journal on this issue, the manufacturer of the measurement devices (Alere) acknowledged that they had been aware of the inaccuracy of their INR measurement devices since 2002 (before the start of the ROCKET-AF trial).[30] INR values at weeks 12 and 24 were measured both, using Alere devices and in a central laboratory. The values obtained should be compared to check whether the inaccuracy of the measurement devices actually had an impact on patient outcomes. The company has not performed any testing as suggested by the BMJ. Given the controversy aroused, some authors have asked the company to disclose ROCKET-AF data to allow for a reevaluation of the trial by independent investigators. Harlan Krumholz, a professor of cardiology at the University of Yale, USA, formally requested the company to provide the complete study data, but Bayer refused to do so.[30]

The reviewers point out that *another missing operational detail concerns the situation of insufficient data or data too ambiguous to allow confidence as to whether the new agent is as effective as the comparator. Again, the fundamental basis of the policy, to prevent harm from the use of inferior therapies, suggests that the proper course is to reject the new therapy if there is not convincing data to support that it is effective as the best feasible comparator*.

Was the trial actually double-blind?

In the ROCKET-AF trial report, it is stated that the study was double-blind, double-dummy. The FDA reviewers, however, noted that the sponsor elected to provide unblinded study data to the Drug Safety Monitoring Board (DSMB) instead of sending blinded data that would be processed by the data managers of the contractor, the Duke Clinical Research Institute.

The company statistician who prepared the unblinded data was ostensibly firewalled. We have no evidence that the firewall was breached, although it could have been breached through informal communications without our knowledge. Complicating the picture is the fact that the statistical analysis plan (SAP) was not drafted until almost a year after the start of enrollment. The SAP was then revised several times, with the last revision occurring shortly before data lock. These practices create opportunities for unblinding.[31]

Making-up of data in trials with rivaroxaban for other indications

In April 2015, Professor Charles Seife published a research study on FDA reviews of several trials and their results.[32] To such purpose, Prof. Seife conducted a cross-sectional study on publicly available documentation published between 01/01/1998 and 30/09/2013 describing FDA visits to clinical centers, where objectionable misconducts were detected.

Malpractices were discovered by the FDA in a total of 57 trials (one or more problems) including: Fabrication or submission of false information: 22 trials (39%); problems with adverse event reporting: 14 trials (25%); protocol violations: 42 trials (74%); inadequate or inaccurate recordkeeping: 35 trials (61%); failure to protect patient safety and/or deficiencies in supervision or informed consent procedures: 30 trials (53%) and other malpractices: 20 trials (35%). Of the 78 trials where severe violations had been detected during FDA inspections, violations were mentioned in only three (4%) of the publications resulting from these trials. Following FDA inspection, no corrections, retractions, expressions of contrition or concern or any other comment in relation to such misconduct were published.

In this study, data were collected from four pivotal trials with rivaroxaban for the prevention of venous thromboembolism in hip surgery that were inspected eight times (the RECORD 1, RECORD 2, RECORD 3 and RECORD 4 trials). Malpractice was detected in all trials, including routine destruction of medical records, non-authorized violation of blinding, fabrication of data, and inappropriate patient randomization. The reviewers found made-up data, problems with adverse event reporting, protocol violations and incorrect recordkeeping, among other malpractices in the four trials. FDA inspectors concluded that the entire RECORD 4 trial was unreliable.

No reports have been published on FDA inspections of the ROCKET-AF trial. Although the results of the inspection have not been disclosed, the FDA is known to have inspected the ROCKET-AF trial, since the investigators of the University of Duke mentioned that 93 patients from a site that had violated good clinical practices had been withdrawn from the trial.[28] Thus, it is deduced that violations of good clinical practice were detected in an inspection.

The finding that unmasking had occurred and subsequent changes had been repeatedly made to the data analysis plan is highly worrying. The fact that rivaroxaban has been developed for other indications under fraudulent conditions –including the fabrication of data– adds uncertainty on the harm/benefit ratio of this drug.

Conclusions on rivaroxaban

Rivaroxaban was approved for atrial fibrillation by FDA authorities against the opinion of FDA reviewers, who deemed that the ROCKET-AF trial did not contribute adequate, quality information proving the non-inferiority of rivaroxaban vs. warfarin.

Also, the deliberate unblinding of the trial by the company, added to the repeated changes made to the statistical analysis plan support concerns about the reliability of the information provided.

The risk of bleeding with the use of rivaroxaban vs. warfarin is probably higher than that reported by the ROCKET-AF trial.

Concerns about apixaban

Fabrication of data in the ARISTOTLE trial

Apixaban was brought to the market after approval based on data from a single pivotal trial called ARISTOTLE.[4] Initially, ARISTOTLE was a non-inferiority study; subsequently, a superiority analysis was performed. The conclusion of the authors was that in patients with atrial fibrillation, apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality.

Professor Seife, provides some data on FDA inspections of the ARISTOTLE trial. Initially, during an inspection at a site in China, FDA inspectors detected that medical records had been manipulated. Had the data from this study site been excluded, no statistically significant differences would have been obtained in mortality. FDA inspectors (*Office of Scientific Investigation*) recommended the withdrawal of this site and another 23 sites in China. Despite FDA recommendations, the full data set was used in the statistical analysis and data from the sites where malpractice was identified were not excluded.[32]

Conclusions on apixaban

The discovery by FDA inspectors that data had been fabricated is a cause of serious concern about the reliability of the information provided by the ARISTOTLE trial, especially when fabricated data were not eliminated from final analysis.

Concerns about edoxaban

Approval of edoxaban was based on the results of the ENGAGE AF-TIMI trial.5 A total of 21,105 patients who underwent a mean follow-up of 2.8 years were included in this study. The objective of this study was to compare the effects of two doses of edoxaban (30 and 60 mg/d) vs. warfarin. The primary endpoint of effectiveness was the incidence of stroke (either ischemic or hemorrhagic) or systemic embolism. The primary endpoint of safety was the incidence of major bleeding. The authors concluded that neither dose of edoxaban was inferior to warfarin for the prevention of stroke or systemic embolism, and the incidence of bleeding and cardiovascular death were significantly lower for edoxaban.

FDA review of the trial[33]

The dosage used in the ENGAGE-AF was based on the results of a previous phase II trial called PRT-018. In this trial, warfarin was clearly underdosed, since 40.5% of patients had an INR<2.0, and 9.3% had an INR>3.0. This means that 50.2% of patients on warfarin were within the therapeutic window. Edoxaban was also underdosed in the phase III ENGAGE-AF trial. The main concern of FDA reviewers was that in ENGAGE-AF, edoxaban was found to be less effective in the prevention of ischemic stroke (at the two doses) in patients with normal renal function.

FDA reviewers proposed two options: a) NOT approving the use of edoxaban and suggesting the company to conduct a trial with adequate drug doses. b) Approving the restricted use of edoxaban only in patients with mild to moderate renal disease and to forbid its use in patients with normal renal function.

Against the opinion of FDA reviewers, FDA authorities approved the unrestricted use of edoxaban.

Table 2. Discontinuation and follow-up rates and differences in primary endpoints in trials with oral antithrombotic drugs (adapted from reference 34).

Trial	Drug	No. of patients	Mean follow-up (months)	Abandonment of therapy (%)	Lost of follow-up patients according to the study report (%)	Lost of follow-up patients according to the FDA (%)	Differences in primary endpoint between study groups (%)
ARISTOTLE	apixaban	18,201	21	25.3	0.4	15	0.6
RELY	dabigatran	18,113	24	21.0	0.1	9	0.7
ENGAGE	edoxaban	21,105	34	33.7	0.005	10	0.9
ROCKET-AF	rivaroxaban	14,264	22	23.7	0.2	22	0.7

New oral anticoagulants and "missing data" in clinical trials

In clinical trials, there are often missing data on the primary endpoint for different causes. To solve this problem, investigators usually assign a dummy value to these patients for statistical analysis. Investigators try to use a reasonable value that is similar to that observed in other patients of the same study group.

This is crucial, since the criteria used to attribute dummy values to missing data clearly affects the final results of the trial.[34] A study assessing the rigor of follow-up of patients in trials with oral antithrombotic drugs has been recently published. This study compares the proportion of patients with missing data according to the trial report and the FDA.

In pivotal trials with apixaban, rivaroxaban, dabigatran and edoxaban, the proportion of lost to follow-up patients as reported in medical journals ranged between 0.005% (ENGAGE trial with edoxaban) and 0.4% (ARISTOTLE trial with apixaban). According to the FDA, the percentage of lost to follow-up patients differed greatly from the percentages published, and ranged between 9% (RELY trial, dabigatran) and 22% (ROCKET-AF trial with rivaroxaban) (table 2).

This means that dummy values were assigned to a significant proportion of patients but were reported as real values. The criteria used for the assignation of dummy values are unknown, which causes uncertainty about the reliability of the conclusions drawn from these trials.

Conclusions

The FDA decisions to approve the use of dabigatran, rivaroxaban, apixaban and edoxaban for atrial fibrillation were based on pivotal clinical trials that were performed with numerous irregularities including the deliberate omission and fabrication of data.

No reliable information is available on the harm/benefit ratio of dabigatran, rivaroxaban, apixaban and edoxaban for atrial fibrillation *vs.* warfarin.

By approving the use of these drugs, regulatory agencies showed a worrying lack of rigor, since they ignored the serious deficiencies and fabrication of data detected by their own inspectors in pivotal trials.

Regulatory agencies should make complete data from trials publicly available to ensure transparency and provide reliable information. This would allow for the optimization of choice of treatments.

Acknowledgements

We are grateful to James M Wright of the University of British Columbia, Canada, for reviewing the text.

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