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EXPERT OPINION

Dose tailoring of dabigatran etexilate: obvious or excessive?

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Introduction: Dabigatran etexilate is used for preventing blood clots and tends to replace older anticoagulants in many of their indications. However, the 'one dose fits all' policy is subject to criticism. Recent findings assert the anxiety of the scientific community concerning the pharmacokinetic properties of dabigatran etexilate, that is, an important interindividual variability including an important genetic variant with a significant dependence of the renal function as route of elimination.

Areas covered: This meta-opinion provides an overview of the current knowledge and evidence on the dose tailoring of dabigatran etexilate. It also discusses the remaining challenges to benefit from this perspective strategy to enhance the benefit–risk balance of dabigatran etexilate. Data were searched in the published literature and on regulatory agencies' websites. Additionally, unpublished data were searched and discussed.

Expert opinion: Causality between dabigatran exposure and bleeding risk is now established and recommendations on how to best estimate the drug exposure are published. Additionally, simulating studies revealed that a dose adaptation based on dabigatran plasma concentration estimations could improve the benefit–risk profile of the drug. This accumulating evidence suggests that some patients under dabigatran etexilate may benefit from a tailoring of the dose beyond the ones already proposed by the manufacturer.

Keywords: anticoagulant drugs, benefit–risk assessment, dabigatran etexilate, drug monitoring

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1. Introduction

In a recent viewpoint, Powell JR stressed out the interest of having the possibility to tailor the dose of the different direct oral anticoagulants (DOACs) based on biomarker tests. The author suggested that '*individualized DOAC dosing may benefit to drugs with greater interpatient variability in pharmacokinetics or pharmacodynamics, patients who do not have average characteristics, when other factors change or when patients have multiple characteristics that could affect dosing*' [1]. To date, accumulating evidence point out the possibilities to improve the benefit–risk profile of these compounds, especially for dabigatran etexilate (Pradaxa®) – a direct oral thrombin inhibitor [1,2].

Since its launch, several cases of major bleeding including some with fatal outcomes were reported post-marketing in the literature [3] or directly to the adverse event databases worldwide. Interestingly, an evaluation of bleeding reports in the FDA Adverse Event Reporting System during the first year of approval of dabigatran etexilate suggests that fatal outcomes are higher in clinical practice than they were in controlled clinical trials [4]. However, as underlined by Southworth *et al.*, these case reports might have reflected a greater likelihood of reporting a bleeding event in a patient receiving dabigatran etexilate than in one receiving warfarin; in addition, life-threatening major bleedings are more likely to be reported than less

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Article highlights.

- Dabigatran etexilate is at least as efficacious as the standard of care in the various indications.
- Dose tailoring was suggested based on several re-analyses of the RE-LY study.
- Several groups of experts have already proposed recommendations regarding when and how to perform anticoagulant activity or concentration measurements.
- Recent findings strengthen the questioning of the scientific community concerning the 'one dose fits all' policy.
- Simulating data suggests that a dose tailoring based on early assessment of the response at the individual level might improve the benefit–risk profile of dabigatran.
- Well-designed randomized controlled trial is required to provide clear insights in this field.

This box summarizes key points contained in the article.

serious cases, leading to some bias. The FDA thus compared bleeding rates for dabigatran etexilate and warfarin using insurance-claim data and administrative data from the FDA Mini-Sentinel database [5]. They mentioned that results reflect those of the large Phase III study in nonvalvular atrial fibrillation (NVAF), that is, that bleeding rates with dabigatran etexilate did not appear to be higher than those with warfarin. However, the lack of adjustment for confounding variables and the lack of a detailed medical record review are some weaknesses of this analysis that need to be highlighted. Therefore, in order to address some limitations of the Mini-Sentinel analysis, the FDA is currently conducting two protocol-based assessments, using claims data from Mini-Sentinel and other claims databases, in which adjustments will be performed for confounding factors.

Out of the FDA investigation, a recent analysis of Medicare beneficiaries found opposite results [6]. The authors reported that in the real-world clinical practice, after adjusting for patient clinical and demographic variables, dabigatran was associated with a higher incidence of major bleeding regardless of the anatomical site [6]. Another investigation from a large US database reported that, compared to warfarin, the risk of major bleeding was not different among the two groups, but a lower risk of hemorrhagic stroke and higher risk of gastrointestinal bleeding was seen with dabigatran etexilate. Importantly, although the risk of stroke is reduced with dabigatran etexilate, it is still twice the one reported in the RE-LY study, thus suggesting that real-life patients do not benefit from dabigatran etexilate to the same extend than in the RE-LY study [7]. In the meantime, other registries such as the GARFIELD, the GLORIA-AF or the ORBIT-AF also aim at expanding the real-life knowledge of antithrombotic utilization in patients with AF [8-10]. These reports raised concerns about the necessity of an individual monitoring to identify poor or high responders.

2. Current evidence

2.1 Rationale for dose tailoring

Dabigatran etexilate is an oral prodrug, rapidly converted by esterases, notably liver esterase *CES1*, to dabigatran, a reversible direct thrombin inhibitor. The pharmacokinetic properties of the prodrug are characterized by a large interindividual variability in the bioavailability (3 – 7%) [11]. Moreover, the active metabolite dabigatran is mainly eliminated by the kidney. Its clearance is therefore highly dependent on any fluctuation of the renal function [12,13]. This led the regulatory authorities to recommend an evaluation of the renal function by calculating the creatinine clearance, using the Cockroft–Gault method, prior to the initiation of the treatment.

Until recently, data on a possible correlation between the drug exposure and clinical outcomes were lacking although requested by experts in the field [14]. A reanalysis of the RE-LY study by Reilly *et al.* showed that ischemic stroke and bleeding outcomes were correlated with dabigatran plasma concentrations [15]. It was revealed that both doses of dabigatran etexilate tested in the RE-LY study were associated with an impressive fivefold variation from 10th to the 90th percentile of the dabigatran plasma range concentration. Another recent study confirmed these results whether blood samples were taken at trough or at peak [16]. As expected, renal function was the predominant characteristic that determined plasma concentration. In the study of Reilly *et al.* both safety and efficacy outcomes were correlated with plasma concentrations, whereas demographic characteristics (mainly age and previous stroke) played the strongest role in determining risk of clinical events. The authors concluded that for patients at highest risk events, such as the very elderly and/or those with poor renal function, a tailoring of the dose might improve the benefit:risk ratio if they are at one or the other extreme of the concentration range [15]. Additionally, in a subgroup analysis of the same RE-LY study, genetic variants were investigated to explain a part of the interindividual variability [17]. Paré *et al.* showed that the rs2244613 single nucleotide polymorphism (SNP) intronic to the esterase gene *CES1* was associated with a decreased trough concentrations and a decreased risk of bleeding. Interestingly, this SNP was present in 32.8% of the white European ancestry participants of this study. No difference was found regarding the efficacy of dabigatran etexilate. The authors conclude that routine genotyping may enable clinicians to tailor the dose of dabigatran etexilate for individual patients and thereby optimize the balance between efficacy and safety [17]. These preliminary pieces of evidence already suggest the importance of assessing the individual response of such patients.

2.2 Position of the regulatory agencies

At the time of the submission of the marketing application for the prevention of stroke and systemic embolism in patients with NVAF, the FDA and the European Medicines Agency

made their decisions based on the results of the RE-LY trial, which demonstrated the benefits and risks of unmonitored dabigatran versus dose-adjusted warfarin.

However, the Clinical Pharmacology and Biopharmaceutics Review(s) (NDA 22-512) of the FDA, first released in September 2010 (i.e., before the marketing authorization in US), already informed about the correlation between safety and efficacy outcomes from the RE-LY study and dabigatran plasma concentrations [13]. It is, indeed, clearly stated that '*going from the 10th to 90th percentile of observed pre-dose dabigatran concentrations (22.9 – 238.3 ng/ml) in RE-LY, the probability of a major bleed within 1 year in a typical patient is predicted to increase from 0.27% to 1.82%, while the probability of an ischemic stroke within one year in a typical patient is predicted to decrease from 1.05% to 0.52%*' [13]. Once implemented together, these figures suggest that exceeding 200 ng/ml at C_{trough} will increase the risk of bleeding without supplemental protection against stroke. This is in line with the data published by Reilly *et al*. In addition, in patients with severe renal impairment, the FDA recommends to reduce the dose to 75 mg twice daily (b.i.d.). Importantly, this dose has not been tested in clinical trial in patients with NVAF and this population was excluded from the RE-LY study for safety reasons. Furthermore, based on simulations studies provided in the Clinical Pharmacology and Biopharmaceutics Review(s) (NDA 22-512), a dose of 75 mg/day was recommended, whereas in the Summary Review and the Labeling Information, the recommended dose is 75 mg b.i.d. [13]. The rational behind the selected dose regimen is clearly not provided, making a transparent assessment of the efficacy of the 75 mg b.i.d. strategy in NVAF patients quite difficult. The availability of an intermediate dose, that is, the 110 mg b.i.d. dose regimen, would have provided an option for high responders in whom the 75 mg b.i.d. dose regimen cannot be recommended.

The EU-Summary of Product Characteristics (SmPC) recommends the use of the 110 mg b.i.d. dose regimen in patients aged > 80 years and those who receive concomitant verapamil, a potent P-gp inhibitor. In patients aged between 75 and 80 years, with moderate renal impairment, with gastritis, esophagitis or gastroesophageal reflux, and other patients at risk of bleeding, the dose reduction should be selected based on an individual assessment of the bleeding and thrombotic risk [18]. This allows tailoring more precisely the dose of dabigatran etexilate in frail patients. In addition, concerns had been raised by the European Medicines Agency regarding the large variability in plasma levels and bleeding risk. Specific test thresholds associated with an increased risk of bleeding at C_{trough} were requested and are now provided in the EU-SmPC. This document highlights that exceeding the 90th percentile of dabigatran trough levels (i.e., 200 ng/ml) is considered to be associated with an increased risk of bleeding [18]. Moreover, in the assessment report of the Committee for Medicinal Products for Human Use on the extension of the indication to stroke prevention in NVAF (date release: 9 June 2011) [19], it was indicated that '*anticoagulation measurement has been requested at the time of the initial marketing authorization application:* [1] *to better assess the drug during its clinical development,* [2] *to provide tools to manage patients in real-life in situations of increased bleeding risks, when event is observed or when it is foreseen to occur (drug interactions, overdoses, surgery, special populations)*'.

Several groups of experts have already proposed recommendations regarding when (**Table 1**) and how to perform anticoagulant activity or concentration measurements [20-23]. The activated partial thromboplastin time was initially proposed to estimate the dabigatran's intensity of anticoagulation but presents an inter-reagent variability and does not correlate well with dabigatran concentrations. Hence, a calibrated dilute thrombin time, which has achieved the CE mark and is commercially available in Europe, is proposed to accurately estimate the plasma dabigatran concentration ranging from 50 to 500 ng/ml [19,24]. New methodologies even allow an accurate measurement until < 10 ng/ml [25]. Unfortunately, the FDA has not yet approved this test and mass spectrometry thus remains the only method that can ensure accurate plasma concentration measurements [24]. Importantly, the Committee for Medicinal Products for Human Use assessment report mentioned that these tests can be used to decrease the dose in case of increased exposure, but never to increase the dose in case of lower exposure [19]. Moreover, the European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with NVAF stressed out the fact the quantitative assessment of the drug exposure may be needed in emergency or in special clinical situations. They also recommended dose adaptations when several interfering factors are present in one individual but acknowledged that information is not available yet for many potential interactions with drug often used in AF patients [26]. This strongly highlights that, in several cases not studied in clinical trials, we cannot assert that these patients are not accumulating the drug to a level associated with an increased risk of bleeding and the current absence of commercially available antidote precludes urgent reversal of the anticoagulant activity [26]. Inversely, we cannot warrant sufficient protection against stroke or thromboembolism with interfering factors that would enhance the clearance of the drug.

2.3 Lack of transparency

During US litigation proceedings, Boehringer Ingelheim was asked to release its internal investigation on plasma level adjustment [27]. Its assessment, based on the RE-LY sub-study, identified an expected therapeutic range for dabigatran in the setting of NVAF. The company found that plasma concentration at C_{trough} (i.e., 12 h after the last intake) between 90 and 140 ng/ml provided the best benefit:risk ratio between prevention of stroke and occurrence of bleedings [27]. The design of this simulation study was proposed as followed: after 1 week of standard treatment with dabigatran etexilate 150 mg b.i.d., measurement of plasma drug level is performed at C_{trough}.

Table 1. Summary of patients/situations that could benefit from a monitoring of plasma concentrations and/or a dose tailoring.

Bleeding or recurrence of thrombosis
Before an invasive procedure (elective or urgent surgery)
In patients with potential drug interactions that affect the pharmacokinetics of dabigatran etexilate such as P-gp inhibitors or inducers
In patients with genetic mutations (i.e., rs2244613 minor allele carriers)
In patients with extreme body weight (< 50 or > 110 kg)
In elderly patients (> 75 years of age)
In case of accumulating interfering factors

Three different algorithms were proposed based on doses available on the market. For patients with plasma concentrations < 90 ng/ml, between 90 and 140 ng/ml and > 140 ng/ml, the 150, 110 and 75 mg b.i.d. dose regimen were proposed, respectively. The treatment period was ~ 20 months and the simulation includes 5000 patients. The results showed that 29.9 and 25.5% of the patients would require the 110 and 75 mg b.i.d. dose regimen, respectively. This algorithm shifted the exposure since the median C_{trough} was reduced by 21%, whereas the minimum exposure was unchanged and the 90th percentile was significantly reduced [27].

Regarding the clinical outcome, they found that compared with the reference treatment (i.e., 150 mg b.i.d.), the risk of ischemic stroke and systemic thromboembolism events was comparable (relative risk = 1.06; 90% CI = 0.76 – 1.50), whereas the risk of major bleeding is significantly reduced (relative risk = 0.80; 90% CI = 0.66 – 0.97). Compared to warfarin (n = 4597), the risk of ischemic stroke and systemic embolic events showed a trend for reduction (relative risk = 0.80; 90% CI = 0.58 – 1.11), whereas the risk of major bleedings is significantly reduced (relative risk = 0.60; 90% CI = 0.50 – 0.72) [27]. These results clearly highlighted the benefits in adjusting doses to optimize plasma level of anticoagulation.

3. Conclusion

The recent findings strengthen the questioning of the scientific community concerning the 'one dose fits all' policy for dabigatran etexilate. The pharmacokinetic properties of dabigatran etexilate were already highlighted and a proper drug monitoring had been proposed in several cases. Causality between dabigatran exposure and bleeding risk is now established; simulation data provide model to best manage patients and potentially improve outcomes, and recommendations on how to best perform estimations of drug exposure are published. This accumulating evidence reveals that some patients under dabigatran etexilate for chronic treatment may certainly benefit from a tailoring of the dose probably beyond the ones already stipulated in the different regulatory SmPCs. This is likely to enhance the benefit–risk balance of dabigatran etexilate. Taken together, this information suggests that, since the marketing authorization, monitoring the plasma concentrations of dabigatran in certain patients was recognized as a risk minimization to improve the benefit:risk ratio of the product.

4. Expert opinion

This meta-opinion was focused on dabigatran etexilate since, to date, this agent is the one for which the most data are available. However, the rationale can easily be expanded to other DOACs. The debate concerning the monitoring of these drugs is not new, with supporters of the pros and cons [28,29]. Indeed, several criteria should be taken into consideration when considering a proper drug monitoring: a high i) intra- and ii) inter-individual variability in drug level, both justifying identification of the optimal dose for each patient at the start of treatment; iii) a low variability and good reproducibility in the assay method; iv) a correlation between drug level and clinical event; and v) the demonstration of the value of the therapeutic drug monitoring [29].

Concerning dabigatran etexilate, the intra- and inter-individual variability in drug levels has been demonstrated with these molecules while techniques to ensure plasmatic measurements are now commercially available, at least in Europe. Results from the RE-LY study indicate a correlation between dabigatran exposure and bleedings and thus, the only remaining issue consists on the demonstration of the benefit of therapeutic drug monitoring. To our knowledge, no supplemental post-authorization efficacy and safety trials directly comparing laboratory based dose-adjusted versus unmonitored dabigatran etexilate therapy in NVAF population have been requested/launched. Some investigations had been performed in order to identify poor and high responders among typical AF population [15,16]. Unfortunately, these analyses suffered from several limitations [30,31]. Indeed, the monitoring of these patients should take into account the rapid clearance of this drug (i.e., half-life of ~ 13 h), depending on the renal function [11,18] and therefore, strict protocols are needed to avoid biased results. In addition, in each of these 'diagnostic' studies, clinical outcome must be collected and correlated with the pharmacokinetic profile of the patient. There is, to date, no clear consensus regarding when to perform such measurement and when is the best time for sampling. However, sample taken at trough steady state seem to be the appropriate choice to correctly reflect the response at the individual level since the trough value can be easily captured and also because harmful threshold are provided for this sampling period.

Thus, a well-designed study is still needed to provide strong recommendations in this field. However, if such a study is envisaged, power calculations are necessary in order to accurately assess the benefit of this approach. Simulation data already suggested that compared to the reference treatment (i.e., 150 mg b.i.d. in NVAF patients), titration of dabigatran etexilate may reduce the rate of major bleedings from 4.38 to

3.49% (absolute event rate – not annualized) [27]. Allowing an α error of 5% and a statistical power of 80%, it will be needed to include nearly 6000 patients in each group to see a statistical difference between these two types of intervention. The major concern is that, without the input of the different regulatory authorities, it is unlikely that the drug company will move into this direction and sponsor this investigation.

Pending the establishment of such researches, testing should be envisaged in each patient in whom the therapeutic response is not optimal or in which the establishment of the intensity of anticoagulation is primordial for safety issue, as summarized in **Table 1**. Repeated measures can be proposed each time a new interfering factor is identified to ensure an accurate response.

Testing should also be proposed with the other DOACs. Indeed, a similar association between plasma concentrations and clinical outcomes has been identified with edoxaban, a direct factor Xa inhibitor [32]. For rivaroxaban and apixaban, data are still lacking even if the FDA Clinical Pharmacology and Biopharmaceutics Reviews of these molecules clearly suggest an association between drug exposure and safety outcomes [33,34]. However and importantly, factors other than the plasma concentration could also affect the benefit–risk profile of these drugs and the therapeutic range would probably not be the same for each category of patients. Namely, in the ENGAGE AF-TIMI 48 trial, comparing edoxaban with warfarin for stroke prevention in patients with NVAF, patients who met the criteria for a dose reduction have higher bleeding rates compared to those in whom the dose was not reduced, despite lower edoxaban concentration at trough [32].

In conclusion, we are convinced that blood coagulation testing will improve the benefit–risk profile of dabigatran etexilate and probably other DOACs by identifying poor and high responders. Further investigations based on the comments raised through this meta-opinion are still required in order to improve the efficacy and safety of the DOACs.

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J Douxfils, M François and D Jean-Michel are contributed equally to this work.

Declaration of interests

M Francois has acted as consultant for Boehringer Ingelheim, Bayer Healthcare, Bristol Meyers Squibb and Pfizer. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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