Closing the information gap between clinical and postmarketing trials: the case of dabigatran

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The outcomes of postmarketing studies on a novel drug are often less favourable than those of the drug’s phase III trials. Several causes underlie this discrepancy—often methodological by nature, many of which may be unavoidable. However, one avoidable caveat is overlooked too often: if participants of phase III trials differ markedly from the patients who will receive the drug, it may take years before all the clinical effects of the drug are properly known. New postmarketing studies have shown that this is arguably the case for dabigatran, a novel oral anticoagulant (NOAC) used to prevent ischaemic stroke in patients with non-valvular atrial fibrillation (NVAF).

Currently, physicians treating patients with NVAF are faced with an important decision: whether to prescribe traditional oral anticoagulants, in the form of vitamin K antagonists (VKAs) like warfarin, or to start with an NOAC. The focus of our paper is on dabigatran, a direct thrombin inhibitor, because it was the first NOAC that appeared on the US market in 2010, and is the most prescribed and most thoroughly researched NOAC thus far.1 However, the discussion presented here may also apply to the other NOACs currently on the market (the direct factor Xa inhibitors Apixaban, Edoxaban, and Rivaroxaban). Results from the phase III trial on dabigatran, called the RE-LY trial, suggest that dabigatran 150 mg b.i.d. is more effective in preventing ischaemic stroke than VKAs, with a lower risk of intracranial haemorrhage.2 Dabigatran 110 mg b.i.d. is found to be equally effective as VKAs in the RE-LY trial, with less bleeding complications. However, this dose has not been approved for the USA.

Although the results from the RE-LY trial were positive, it is questionable whether dabigatran is the best option for stroke prevention in some or even many NVAF patients. A recently published postmarketing study has shown that dabigatran causes a significantly higher risk of extracranial bleeding than VKAs in clinical practice.3 It was also found that NVAF patients using VKAs for the secondary prevention of stroke have a two-fold risk of suffering an ischaemic stroke when switching to dabigatran.4 This apparent discrepancy between the results of the RE-LY trial and postmarketing studies on dabigatran is partly attributable to the selection of the participants for the RE-LY trial.5 In Table 1, we have outlined some of the major differences we have found between RE-LY participants and the total population of NVAF patients in the USA.

In phase III trials such as the RE-LY trial, participants usually have to meet strict inclusion and exclusion criteria. There are a number of reasons for this. First, researchers aim to exclude individuals with comorbidities that could mask the true effect of the drug through a less favourable signal-to-noise ratio. Second, researchers and physicians have a moral obligation to protect subjects who could be more susceptible to adverse effects, such as the elderly or patients with renal failure. As a result, drug research is performed in a suboptimal sequence of steps: (1) phase III clinical trials are performed in relatively young and healthy individuals, mostly male; (2) the drug is approved, the results from the trials are generalized, and prescriptions are provided for the total patient population; (3) adverse effects are observed in individuals or subpopulations, and further research on the limitations of the drug is performed; (4) guidelines and restrictions on prescribing the drug are developed on the basis of these post-approval studies. In rare cases, the drug is even withdrawn from the market afterwards.

Researchers and policy-makers are thus faced with a moral dilemma: (1) either apply strict exclusion criteria to participants in phase III trials—with the risk of unknowingly exposing some patients to drugs that are unsafe or ineffective for them until postmarketing experience alerts us to the dangers—or (2) include study populations in phase III trials that adequately represent the target population of the drugs—with the risk that some vulnerable study subjects are exposed to serious side-effects during the trials. Opting for strict selection criteria (Option 1) is consistent with upholding the precautionary principle primum non nocere (‘first, do no harm’). Essentially then, option 1 follows a deontological point of view: one complies with a duty or rule.

Option 2 might violate the precautionary principle, but could be justified by pointing out that (1) it provides the fastest way to obtain complete insight into the effects of a novel drug, including patient heterogeneity in response to the drug and (2) the controlled environment of the trial ensures that side-effects of the drugs are.
Table 1  Discrepancies between the patient population with atrial fibrillation in the USA and the study population of the RE-LY trial, and the implications of these discrepancies for the effectiveness of dabigatran in comparison with vitamin K antagonists in real clinical practice

<table>
<thead>
<tr>
<th>Factor</th>
<th>Proportion or mean in all AF patients in the USA</th>
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<tbody>
<tr>
<td>Adherence and drug half-life</td>
<td>Data on adherence of DBG in real clinical practice are not available</td>
<td>Data on adherence of DBG during the RE-LY trial are not available</td>
<td>There is a higher rate of non-adherence in real clinical practice. Because DBG has a shorter half-life than VKAs, non-adherence will have a stronger impact on the effectiveness of DBG than that of VKAs.</td>
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<td>Age</td>
<td>The mean age in a sample of AF patients aged 65 years or older was 79 years. All (or almost all) participants of the RE-LY study were 65 years or older, with a mean of 71.5 years</td>
<td>Of all VKA users in the RE-LY trial, 41% used aspirin at baseline</td>
<td>The risk of major bleeding increases with age inDBG users but not in VKA users. Because the age of AF patients is higher in real clinical practice than in the RE-LY trial, the risk of major bleeding with DBG was underestimated in the RE-LY trial.</td>
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<td>Antiplatelets</td>
<td>The share of antiplatelet users at baseline in a sample of newly diagnosed AF patients was 8%. The share of antiplatelet users at baseline in a sample of AF patients aged 65 years or older was 17%.</td>
<td>The median BMI of the RE-LY study population was 28</td>
<td>The risk of bleeding with VKAs is higher when also using aspirin. It is possible that this concomitant drug use is less common in real clinical practice than in the RE-LY trial. Therefore, the risk of bleeding with VKAs could be underestimated in the RE-LY trial.</td>
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<td>BMI/weight</td>
<td>The mean BMI of a sample of newly diagnosed AF patients was ±29.</td>
<td>The share of women in the RE-LY study population was 36%</td>
<td>DBG is less efficacious in AF patients with a higher BMI or weight. Consequently, it is unclear whether DBG or a VKA is the better choice for AF patients who are overweight.</td>
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<td>Chronic kidney disease</td>
<td>The share of patients with chronic kidney disease in two samples of AF patients aged 65 years or older was 9 and 13%, respectively. The share of patients with chronic kidney disease in a sample of newly diagnosed AF patients was 33 and 10%, respectively.</td>
<td>NVAF patients with chronic kidney disease were excluded from the RE-LY trial</td>
<td>DBG users with chronic kidney disease have a higher risk of bleeding. It is unclear whether it is safe to prescribe DBG to NVAF patients with chronic kidney disease.</td>
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<td>Gender</td>
<td>The share of women in two samples of AF patients aged 65 years or older was 55 and 52%, respectively. The share of women in two samples of newly diagnosed AF patients was 59 and 42%, respectively.</td>
<td>The share of women in the RE-LY study population was 36%</td>
<td>The efficacy of DBG vs. VKAs is higher in women than in men, although women also have a slightly higher risk of bleeding with DBG use. Because women were underrepresented in the RE-LY trial, the effectiveness and risk of bleeding of DBG were underestimated.</td>
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<td>Heart failure</td>
<td>The share of patients with heart failure in two samples of AF patients aged 65 years or older was 36 and 18%, respectively. The share of patients with heart failure in a population of newly diagnosed AF patients was 51 and 32%, respectively.</td>
<td>32% of the RE-LY study population had heart failure</td>
<td>DBG is less efficacious in patients with symptomatic heart failure. It is unclear whether DBG is less effective in patients with asymptomatic heart. It is therefore unclear whether it is better to prescribe DBG or VKAs for AF patients with heart failure.</td>
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<tr>
<td>Previous stroke and prior VKA use</td>
<td>The share of VKA users with a previous stroke or transient ischaemic attack (TIA) in two samples of newly diagnosed AF patients was 23 and 9%, respectively. Because these samples include newly diagnosed AF patients only, it is plausible that the share is larger in the US population of AF patients.</td>
<td>20% of the RE-LY study population suffered a previous stroke or TIA. Around 50% of DBG users had been on long-term VKA therapy at baseline</td>
<td>One study found that patients who suffered a prior stroke/TIA and switched from VKAs to DBG had a two-fold risk of ischaemic stroke compared with those staying on VKAs. It is unclear whether the share of patients who suffered a previous stroke or TIA and also made a switch from VKAs to DBG in the RE-LY trial (estimated 10%) adequately reflects the share in real clinical practice.</td>
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<td>Menorrhagia</td>
<td>The risk of vaginal bleeding is higher with DBG than with VKAs.</td>
<td>Premenopausal women were not included in the RE-LY trial</td>
<td>Menorrhagia is an additional risk factor for premenopausal women. It is therefore unclear whether it is safer to prescribe DBG or VKAs to premenopausal women with AF.</td>
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formed, in which some patients suffering from cardiac arrest were harms. Randomized controlled trials (RCTs) were therefore per-
whether the acute benefits of epinephrine really outweigh its plays a role in many clinical studies, and becomes increasingly consequentialist view. The dilemma between deciding on the basis leading here, and not a rule or duty, this strategy expresses a more complex and profound in case of more severe illness.
For example, administration of epinephrine has been recom-
more readily identified and managed. Since the consequence is leading here, and not a rule or duty, this strategy expresses a more consequentialist view. The dilemma between deciding on the basis of overall consequences or uncompromising adherence to principles plays a role in many clinical studies, and becomes increasingly complex and profound in case of more severe illness.

For example, administration of epinephrine has been recom-
mended in international guidelines for the treatment of patients with cardiac arrest for many years, even though it is unclear whether the acute benefits of epinephrine really outweigh its harms. Randomized controlled trials (RCTs) were therefore performed, in which some patients suffering from cardiac arrest were allocated to a control group receiving a placebo instead of epinephrine.14,15 Here, the same questions apply as those with regard to dabigatran: (1) What is it that we would want to know, before making these treatments more widely available? (2) What sort of research is needed in order to obtain such knowledge? (3) Can the conduct of such studies themselves be justified? Considering that the inclusion of extremely vulnerable patients (those suffering from life-threatening cardiac arrests) in RCTs were considered appropriate, it is surprising to see that it was decided otherwise in the case of the RE-LY trial.

There is still considerable uncertainty on the effectiveness and safety of dabigatran. First, the many exclusion criteria ruled out patients with anaemia, chronic kidney disease, liver disease, and those with previous bleeding events, such as gastrointestinal or intracranial bleeding.18 Second, the RE-LY study population was not an adequate reflection of the US population of AF patients, as the proportions of older patients, women, and patients with chronic kidney disease were underrepresented. On the other hand, the time in therapeutic range of VKAs was relatively high in the trial (64.4%), possibly overestimating the effectiveness and safety of the comparator. Third, an insufficient subgroup analysis on the pre-
vention of ischaemic stroke leaves physicians with too little know-
edge on the comparative effectiveness of dabigatran for specific patient groups, such as patients who are overweight or those with a history of stroke and long-term VKA use. Also, the elevated risk of bleeding with dabigatran in older patients, black patients, preme-
nopausal women, and patients with lower renal function could have possibly been revealed before dabigatran’s market entry if the researchers had performed a subgroup analysis with regard to bleed-
ing. Fourth, although the FDA approved the dose of 75 mg b.i.d. for NVAF patients with renal failure, the dose of 110 mg b.i.d. was not approved. A lot of uncertainty still surrounds the 75 mg variant, as it was only tested with pharmacokinetics data and not in human trials. There is also debate on whether the FDA should have disapproved the 110 mg regimen, as this leaves physicians and patients with no option to individually tailor a drug that shows a high variability in drug reaction between patients, mainly due to differences in renal clearance.16,17

Although the uncertainty surrounding dabigatran is partly caused by holding on to a strict interpretation of the precautionary principle in the context of clinical research, the principle is only loosely applied in daily clinical practice. For example, in Denmark recommendations on the use of dabigatran 150 mg b.i.d. set by the European Medicines Agency are not followed in 45% of the cases.18 However, although

Table I  Continued

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<td>Race</td>
<td>The share of white patients in two samples of AF patients aged 65 years or older was 92%. The share of black patients was 6 and 3%, respectively.</td>
<td>No information on race is available from the RE-LY population</td>
<td>The risk of bleeding with DBG is higher in black than in white patients. The RR is even two-fold concerning major bleeds. As there is no information on race from the RE-LY trial, it is unclear whether it is safer to prescribe DBG or VKAs to black AF patients</td>
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<td>Time in therapeutic range</td>
<td>TTR differs per country or region. In the USA, the average TTR was found to be 56.7% in the community setting</td>
<td>Overall, the TTR was 64.4% in the RE-LY trial. The mean TTR was 44% in Taiwan and 77% in Sweden</td>
<td>The effectiveness and safety of VKAs is highly dependent on the TTR. For the total US population, it is plausible that the RE-LY study overestimated the effectiveness of VKAs and underestimated the risk of bleeding with VKAs. It is unclear whether DBG or a VKA is more effective and safe to prescribe in regions with a mean TTR larger than 64.4%</td>
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BMI, body mass index; DBG, dabigatran; INR, international normalized ratio (a marker to measure the clotting tendency of the blood, used for dosing vitamin K antagonists); RE-LY, randomized evaluation of long-term anticoagulation therapy (the phase III trial comparing the efficacy of dabigatran with that of vitamin K antagonists); TIA, transient ischaemic attack; TTR, time in therapeutic range, or: the time a patient spends in optimal VKA dosing (INR is within the target range; between 2.0 and 3.0); VKA, vitamin K antagonist.

1In short, a drug’s half-life signifies how fast the effects of the drug will wear off after intake. Because dabigatran has a shorter half-life, it needs to be taken twice daily. VKAs need to be taken once daily.
2This is most likely the reason why the efficacy of dabigatran is highest in South Asia: the relative risk of ischaemic stroke with dabigatran versus VKAs was 0.21 in South Asia compared with 0.88 in Western Europe. 

26.7% in the community setting13

92%.7,11 The share of black patients was 6 and 3%, respectively.8 The share of black patients was 8 and 5%, respectively.

Overall, the TTR was 64.4% in the RE-LY trial. The mean TTR was 44% in Taiwan and 77% in Swedenb,2

The effectiveness and safety of VKAs is highly dependent on the TTR. For the total US population, it is plausible that the RE-LY study overestimated the effectiveness of VKAs and underestimated the risk of bleeding with VKAs. It is unclear whether DBG or a VKA is more effective and safe to prescribe in regions with a mean TTR larger than 64.4%
researchers should stretch the precautionary principles as far as ethically possible to build a study population that is representative of the target population, we do not argue in favour of totally abandoning precautionary principles in clinical research. For example, it seems justified that pregnant women were excluded from the RE-LY trial. Instead, we urge clinical researchers and regulatory agencies to deliberate on the right balance between precautionary principles and consequentialist implications. We also urge them to ensure that proper subgroup analyses are performed. In the case of dabigatran, the information gap that currently exists can only be narrowed if further postmarketing trials are performed. Within these postmarketing trials however, the dilemma continues: should new trials be designed to investigate the effects of dabigatran in different—often vulnerable—subpopulations, or are registry studies more appropriate? Valuing, explicating, and discussing the moral implications of these questions are not merely armchair philosophy, it is urgently needed to aid the researchers faced with uncertainty that can impact many lives.

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References