The gold standard for studies to change management in clinical practice is the double-blind randomised controlled clinical trial (RCT), or at least an RCT with blinding of the outcome assessment. In 2009, the first large randomised trial of a Non-vitamin K Antagonist Oral Anticoagulant (NOAC) in atrial fibrillation (AF), the RELY trial, was published (1). This study compared two doses of dabigatran with warfarin in over 18,000 patients with AF (with blinded endpoint assessment), and although it was a non-inferiority trial, showed a significant reduction in stroke or systemic embolism, but only with the 150 mg BID dose, and less major haemorrhage with the 110 mg BID dose. There was less intracranial haemorrhage with both doses, but more gastro-intestinal bleeding. The warfarin was well controlled, relatively the INR range of 64 %. This study led to the licensing of dabigatran for use in AF in many countries from 2010. What this has afforded us now is almost 6 years of experience of dabigatran use in AF and quite a number of studies of the outcome of its use in everyday clinical practice.

The results from the routine clinical use of dabigatran or warfarin in everyday practice have been analysed in variety of national, administrative, health insurance or proprietary databases and registries, to provide what has come to be called “real world” data (RWD). Results of these RWD studies have certain advantages over the “unreal world” of RCTs in that they reflect what is actually happening in practice, usually with more liberal inclusion criteria than seen in the pivotal RCTs, and typically providing a broader range of patients with differing stroke risk profiles treated in a broader range of settings. When the results using RWD confirm findings from the RCTs, it provides the clinician with some confidence about the generalisability of RCT findings that are used to formulate recommendations in treatment guidelines.

There are a number of important limitations to analyses of RWD of NOACs, in that patients given the newer drug may differ in important ways from those given warfarin or other vitamin K antagonists (VKA) when the choice is up to the clinician. Some of these differences may be subtle and very difficult to discern using demographics and clinical characteristics derived from databases and registries, and our attempts to statistically correct for these will inevitably suffer from bias and residual confounding. Some of these differences were well summarized in a recent editorial focus providing a review of RWD on NOAC treatment of AF by Potpara (2), accompanying two articles with RWD published in the same issue of Thrombosis and Haemostasis (3, 4). Gaps in translation from trials to clinical practice inevitably occur (5).

Also, the differing labels in the USA, have led to quite different practices in that country, where only the 150 mg and not the 110 mg BID dose is available, with the 75 mg BID dose available for patients with renal insufficiency (this dose is available only in the USA). In most other parts of the world, the 110 mg BID dose is available and widely used. In Europe the 150 mg BID dose is recommended for most patients according to the European label, while the 110 mg BID dose is recommended for older individuals ≥80 years or with higher bleeding risk (HASBLED score ≥3) or with concomitant verapamil. Simulations of use of the European label using the RELY RCT data yielded interesting extrapolations (6), showing superiority in both efficacy (stroke/systemic embolism and mortality) and safety (major bleeding) and a net clinical benefit compared to warfarin. RWD with much larger numbers would be useful to determine whether this advantage might be seen in everyday practice.

It is therefore of interest to have a large systematic review and meta-analysis of dabigatran RWD in AF performed, and published in this issue of the journal (7). There have been previous meta-analyses by the same authors (published in abstract form only) and this year by Romanelli et al. (8), but in the current meta-analysis, Carno et al. extended their previous work with larger numbers of studies. Patient numbers were therefore increased, with over 700,000 included: of these, over 200,000 were on dabigatran and the remainder on VKA, compared with a total of 348,750 patients in the Romanelli et al. meta-analysis (8). The increased numbers have permitted some interesting sensitivity analyses and comparisons to be made, and the confidence intervals for the overall findings have narrowed, so this study is a useful addition to the RWD literature on dabigatran use in AF.

One of the limitations of this study and indeed all RWD of anticoagulants is that...
the adequacy of INR control is usually not included in the studies. In the three studies that reported it, time in therapeutic range was suboptimal (7), with average values of 57%, 53%, and 39%, rather lower than the 64% in the RELY RCT. Unfortunately, this probably reflects what happens in everyday practice in many situations and in many countries, with the notable exception of some northern European countries including Sweden (9).

Ischaemic stroke and death

One of the important new findings in this meta-analysis by Carmo et al. (7) is the significant 14% reduction in ischaemic stroke compared to VKA for the doses of dabigatran combined, and for the 150 mg BID dose. The confidence interval for the 110 mg dose crossed unity, but the striking feature of the forest plot for the 110 mg dose was the large reduction in ischaemic stroke in the two smaller studies in Chinese subjects from Hong Kong (10, 11). These provide additional substance to the notion that there is an East Asian paradox of both hypercoagulability, and increased bleeding with antithrombotic agents (12), so one cannot assume results will be identical to studies conducted in Europeans. In the East Asian patients recruited in the RELY study, similar findings of increased stroke rates and larger absolute benefit of dabigatran were seen (13). The meta-analysis by Wang et al. (14) also suggests that when compared to non-Asians, the Asian subgroup in the randomised trials showed greater efficacy and safety with NOACs.

Another important difference from the previous meta-analysis and also from the RELY RCT was the significant reduction in total mortality of 27% overall, compared to VKA, which was significant for both doses individually, and in the sensitivity analyses conducted in the current meta-analysis. Of note, the European label simulation of the RELY data provided a similar finding on mortality (6).

Bleeding

This study, in common with previous RWD meta-analysis, and the RELY study, showed a highly significant reduction in intracranial haemorrhage for both doses and in combined analysis. This seems to be a consistent feature common to all NOACs (14). It is also reassuring that the effect size is so similar in the real world studies to that noted in the RCTs.

One important new finding for the current RWD meta-analysis by Carmo et al. (7) was the significant reduction in major haemorrhage with both dabigatran doses compared to VKA, amounting to an overall 21% reduction for the combined dose. This particular bleeding endpoint was not examined in the previous meta-analysis.

Gastrointestinal (GI) bleeding was increased 13% for dabigatran overall in this meta-analysis, but this was driven by a significant increase only in the 150 mg BID dose, a finding virtually identical to that seen in the earlier meta-analysis, as well as the RELY RCT. The elderly are particularly prone to gastrointestinal haemorrhage as shown in the previous meta-analysis (8), with those aged 75 or older given 150 mg BID having a 50% increase in GI haemorrhage compared to VKA, while those younger than 75 had no increase in GI haemorrhage. The same directional changes were noted in RELY, though they did not reach significance. Taken together, it seems fairly secure now that dabigatran 150 mg BID will increase GI haemorrhage compared to VKA, but this increase is likely limited to those aged 75 or older, with no increase noted for the 110 mg BID dose.

Myocardial infarction

There has been some controversy regarding myocardial infarction, with a small numerical but non-significant increase in myocardial infarction in both dabigatran groups in RELY compared to VKA (1). There were some definitional problems for the diagnosis of myocardial infarction in that study, but results were not significantly altered by addition of extra infarcts in a re-analysis. Subsequent meta-analysis of RCTs of dabigatran again raised the possibility that dabigatran was not as effective as warfarin in prevention of MI (15).

It is therefore gratifying to note that the current RWD meta-analysis by Carmo et al. (7) shows absolutely no increase in myocardial infarction (hazard ratio [HR] 0.99). One interesting insight arose from an analysis of myocardial infarction in patients who were new users of oral anticoagulant, compared to those who had previously been on VKA, but were switched to NOAC. New users (anticoagulant naïve) had a significantly lower rate of infarction (HR 0.87), while patients who switched from VKA to NOAC had a significantly higher rate of infarction (HR 1.18). This result was mainly due to the results from the Larsen et al. study, with the authors feeling this was possibly related to selecting older patients with comorbidities and with poor adherence to VKA to switch to a NOAC (16).

Quo vadis?

"Real world" data are now fairly mature with large patient numbers for dabigatran compared to the other NOACs, and provide some comfort to the clinician that the findings of the pivotal RELY trial is generalisable to patients in their own practice. The numbers are sufficient to have some confidence that there is not only non-inferiority compared to warfarin, but that there may be superiority of dabigatran in relation to reduction in ischaemic stroke, and mortality. Regarding safety, there is also reassurance that there is likely to be reduced major haemorrhage in addition to the well-documented reduction in intracranial haemorrhage. All this comes at the expense of an increase in gastro-intestinal haemorrhage, which nevertheless seems limited to the elderly using the 150 mg BID dose, which would be avoided if treatment was given according to the European label.

It will be similarly important to see the results from analyses of large numbers in RWD studies for the other NOACs, rivaroxaban, apixaban, and edoxaban, over the coming years, including those from different regions of the world (17) as well as comparative effectiveness and safety studies between the NOACs and VKA.

The latter are already appearing in the literature. For example, the Danish registries reported an independent study of 61,678 patients with non-valvular AF who were naïve to oral anticoagulants: warfarin (n=35,436, 57%), dabigatran 150 mg
(n=12,701, 21%), rivaroxaban 20 mg (n=7,192, 12%), and apixaban 5 mg (n=6,349, 10%) (18). This study by Larsen et al. (18) found no profound differences between standard dose NOACs and warfarin for ischaemic stroke; however, the risks of death, any bleeding, or major bleeding were significantly lower for apixaban and dabigatran compared with warfarin. Similar conclusions were reported by Yao et al. (19), from a large US insurance database which concluded that apixaban was associated with lower risks of both stroke and major bleeding, dabigatran was associated with similar risk of stroke but lower risk of major bleeding, and rivaroxaban was associated with similar risks of both stroke and major bleeding. Dabigatran was associated with higher risk of major bleeding, and rivaroxaban was associated with similar risks of both stroke and major bleeding in comparison to warfarin. Finally, a recent propensity matched analysis from a US claims database focused on safety amongst 45,361 newly anticoagulated AF patients, found that apixaban (HR 0.53; 95% confidence interval [CI] 0.39–0.71) and dabigatran (HR 0.69; 95% CI 0.50–0.96) initiators had a lower risk of major bleeding, compared to matched warfarin initiators (20). Patients initiating rivaroxaban had similar major bleeding risks with matched warfarin patients.

In summary, studies of RWD with the NOACs show remarkable consistency with the RCTs. Notwithstanding that RCTs remain the best way to test an intervention in a controlled manner, RWD provide complementary and supportive evidence, translating what is arguably the “unreal world” to the “real world” of everyday clinical practice. Time will tell as even more evidence accumulates.

Conflicts of interest
B. Freedman has received research grants to undertake investigator-initiated studies from BMS/Pfizer, Bayer, and Boehringer Ingelheim; has been consultant for Bayer, BMS/Pfizer, Boehringer Ingelheim, Servier, AstraZeneca, and Gilead; and has been a speaker for Bayer, BMS/Pfizer, and AstraZeneca. G. Y. H. Lip has been a consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife, and Daiichi Sankyo; and a speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche, and Daiichi Sankyo.

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References