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EDITORIALS

Novel oral anticoagulants for atrial fibrillation

Patients must live with uncertainty until we have independent scrutiny of key trial data

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Warfarin reduces the risk of stroke in patients with non-valvular atrial fibrillation but has limitations: a narrow therapeutic window, the need for regular monitoring, and risks of bleeding and drug-drug interactions. Partly because of these limitations, novel oral anticoagulants (NOACs or non-vitamin K antagonists) have emerged, including direct thrombin inhibitors, such as dabigatran, and factor Xa inhibitors, such as rivaroxaban. These drugs do not need routine monitoring and are subject to fewer drug-drug interactions. Both have evidence of cost effectiveness in stroke prevention,[1] and in 2014, the UK's National Institute for Health and Care Excellence (NICE) recommended that dabigatran and rivaroxaban should be considered as an "option for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation."[2]

Despite this, use of new anticoagulants has proved to be highly variable in patients most at risk, ranging from 4% to 70% in different areas in England.[3] This may partly be attributable to higher perceived costs , clinical uncertainty about the balance of benefit to harm, and the lack of routinely available antidotes in cases of overdose (although this looks likely to change in the future).

Questions remain about the key drivers of this uncertainty. NICE technology appraisals for both dabigatran [4] and rivaroxaban [5] were primarily based on two large, multinational, industry sponsored clinical trials, RE-LY and ROCKET AF.[6 7] RE-LY compared warfarin and dabigatran in 18 113 participants with non-valvular atrial fibrillation; rates of stroke, systemic embolism, and major haemorrhage were (depending on the dose of dabigatran) either the same as or lower than in those taking warfarin. ROCKET randomised 14 264 participants to either rivaroxaban or warfarin; rivaroxaban was non-inferior to warfarin and was associated with fewer fatal bleeding events and fewer intracranial haemorrhages.

However, there were early concerns that the conduct of the RE-LY trial and the quality of the data may be compromised. Specifically, the manufacturer had not fully disclosed information about the potential benefits of monitoring anticoagulation in people taking dabigatran—one of the key selling points is lack of monitoring.[8] The US Food and Drug Administration therefore initially refused to file an approval of the drug for non-valvular atrial fibrillation because of these concerns and requested a review of RE-LY data. This revealed inconsistencies for 3054 participants and identified previously unreported adverse events (32 myocardial infarctions and 69 major haemorrhages).[9]

The validity of the ROCKET AF trial of rivaroxaban has also been questioned.[10] It has transpired that participants randomised to warfarin were monitored using a defective point-of-care device that was subsequently recalled.[11] It is therefore unclear whether participants in the warfarin arm were managed appropriately, giving a possible unfair advantage to rivaroxaban. Cohen's latest investigation highlights that some of the ROCKET investigators raised concerns about the faulty device and that the data and monitoring safety board may not have been fully informed about a safety investigation instigated by Janssen, which was running the trial.[12]

Published trials suggest that novel oral anticoagulants, such as dabigatran and rivaroxaban, are non-inferior to warfarin,[13] a finding replicated in routine data collected from observational cohorts.[14] Yet uncertainty remains about the reliability of the evidence underpinning the pivotal trials. Part of this uncertainty can be traced back to the rapid review approval process, which aims to accelerate the approval of drugs with the potential for significant clinical benefit. However, when a trial's validity is then called into question this may hinder translation, and in some cases, delay wider uptake.[15] Furthermore, oral anticoagulants are one of the highest risk drugs used in outpatient settings, and valid questions have been asked about why ease of use has been a greater focus than the need to improve the safety profile of anticoagulants.[16]

We need to find ways to reduce uncertainty and increase clarity about the balance of benefit to harm. Replication of the results from RE-LY and ROCKET in independent trials would be one approach, but this may take several years. In the mean time, making the data available for independent scrutiny should be a mandatory regulatory requirement, particularly when there are questions about trial rigour. Finally, a detailed independent analysis of unpublished data from clinical study reports, similar to previous analyses of neuraminidase inhibitors,[17] would also help. We have requested the relevant clinical study reports from the European Medicines Agency, and it has become clear that

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there are likely to be challenges for the trial sponsors in condensing large reports into digestible publications.

Although independent replication of trials, data transparency, and detailed analysis of clinical study reports will be arduous and costly, the concerns highlighted by recent investigations have shown how essential these approaches are to increase our confidence in new oral anticoagulants. Meanwhile patients and clinicians must, for now, live with the uncertainty left by the evidence currently available.

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