Commentary

Dilemmas in the use of new oral anticoagulants

J. THACHIL

Department of Haematology, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL, UK

Address correspondence to Dr J. Thachil, Department of Haematology, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL, UK. email: jecko.thachil@cmft.nhs.uk

The advent of the non-vitamin K oral anticoagulants (or Non-Vitamin K oral anticoagulants (NOACs)) have revolutionized the anticoagulation landscape. Patients who require anticoagulation now have freedom from frequent hospital or clinic visits for monitoring, do not have dietary restrictions, minimal drug interactions and lesser risk of intracranial bleeding. However, there are certain clinical scenarios which present dilemmas in the use the NOACs. These include their use in atrial fibrillation (AF) patients restricted to non-valvular cases, the issue of lack of antidotes, management of cerebrovascular accidents while receiving these drugs, and the emerging conundrum of whether drug level monitoring may be necessary for these drugs.

Can NOACs be used for patients with valvular AF?

All the landmark trials with NOACs were conducted in patients with non-valvular AF which has led to the reservation for their use in AF associated with valvular heart disease.¹ What has probably led to this dilemma is the lack of clarity in defining valvular AF. The situation was not helped by the negative outcomes of the trial comparing dabigatran and warfarin in patients with mechanical heart valves.² In this regard, the recent European guidelines have been helpful to reduce confusion by defining ‘valvular AF’ as AF related to rheumatic valvular disease (predominantly mitral stenosis) or prosthetic heart valves.³ This would mean that the other types of valvular heart diseases, such as mitral and aortic regurgitation, and aortic stenosis, do not result in conditions of low flow in the left atrium, and thus increase the risk of thrombo-embolism.⁴ A recent study by Breithardt et al.⁵ is worth mentioning too. They investigated clinical characteristics and outcomes of patients with significant valvular disease in the pivotal trial comparing rivaroxaban with warfarin (excluded patients with mitral stenosis or artificial valve prostheses). They found older patients with more comorbidities in comparison to patients without valvular disease but surprisingly the rates of stroke or systemic embolism were no different although the rates of clinically relevant bleeding was higher with rivaroxaban. This study concluded many patients with ‘non-valvular AF’ have significant valve lesions but have similar stroke-preventive benefit with rivaroxaban compared to warfarin. This should be translated the fear of prescribing NOACs to patients with valvular AF in the absence of rheumatic mitral valve disease or prosthetic heart valves is unfounded.

Is NOACs worse off due to the lack of antidotes?

Despite its effectiveness and convenience, one of the biggest concerns with NOACs is the lack of antidotes. This has dissuaded physicians from prescribing and persuaded haematologists (who are often contacted to deal with bleeding) to discourage the prescription of these drugs. However, in comparison with the conventional oral anticoagulants like warfarin, these drugs do have an advantage that, in the absence of renal impairment, their anticoagulant effect is short-lasting.⁶ Second, although the incidence of bleeding is similar (better with apixaban)
to warfarin, the dreaded complication of intracranial bleeding is much reduced in comparison with warfarin. Third, even in those patients who developed bleeding, the mortality in patients who received NOACs was significantly less in comparison with warfarin (9.1 vs. 13%). Lastly, the fear of lack of antidote has not discouraged the widespread use of low molecular weight heparins and fondaparinux which do not have a complete reversal agent. On the horizon, there are anticoagulants in development (antibody that blocks dabigatran, dummy factor X which will bind to and block the anti-Xa agents and a universal haemostatic agent which reverses all known anticoagulants), however, which may be useful in the setting of emergency surgery more than bleeding.

How do you deal with NOACs and a new-onset vascular event?

A new onset vascular event like cerebrovascular ischaemia can happen in patients receiving the NOACs, similar to those patients treated with warfarin (albeit rarely). Since thrombolysis could be life-saving and indeed associated with better long-term outcomes, it would be prudent to consider this treatment in such patients receiving anticoagulants too. In this situation, the ability to monitor warfarin with an international normalized ratio (INR) is helpful with many physicians considering thrombolysis if the INR is less than 1.5. This is clearly not possible in the case of NOACs where there are no easy tests to guide such an intervention. However, there are an increasing number of case reports which deal with such a clinical scenario. The European Heart Rhythm association (EHRA) practical guide on the use of new oral anticoagulants state that ‘thrombolytic therapy cannot be given within 48 h after the last administration of NOAC, but this is an arbitrary recommendation, which has yet to be tested.’ Although this is a safe approach, it is possible that at least in the stroke units, if the appropriate laboratory methods can be arranged, thrombolytic therapy can be considered in selected patients. A proposed algorithm is given in the Figure 1.

Do NOACs need drug level monitoring?

Several experts have suggested the need for monitoring plasma levels of NOACs in certain clinical situations. The issue of monitoring became ‘inflammatory’ with a recent publication in the British Medical Journal, where the manufacturers of dabigatran were accused of not disclosing information about the need for monitoring in their trial. Although monitoring of the drug levels is possible in specialized laboratories, what is not clear is the next step in management based on these levels. Does a low or high level in comparison to the published trial data means that we should increase or decrease the doses of these agents? In the least, this is problematic because all of these drugs have fixed dosages allowing little possibilities in increasing the doses (although lower doses may be possible, e.g. dabigatran 110 mg, Rivaroxaban 10 mg, Apixaban 2.5 mg). On the other hand, if we reduce or increase the dose based on the levels, do they translate to better effectiveness or safety? There are only two clear situations where levels monitoring may be clinically helpful i.e.; to ensure clearance of the drug in the need of an emergency procedure (like need for thrombolysis) and to ensure compliance. In the cases of overdoses or renal impairment, level monitoring is unlikely to change the clinical management where routine clotting tests can aid in identifying clearance. In the cases of bleeding, once again, drug levels are unlikely to be helpful in deciding the haemostatic support much more than the information obtained from clinical bleeding. In older individuals or patients with extremes of body weight, unless the levels are extremely high, where decreases to the lower dose may be considered, it is probably prudent to consider alternatives to NOAC. In these situations, however, it has not been shown
whether the lower doses are as effective as the standard dosing.

In summary, dilemmas still exist in the best way to deal with NOACs. But several unfounded fears can be put to rest and physicians should feel confident to embrace these drugs, which are certainly more convenient for patients. More prescriptions will hopefully lead to more confidence in their use.

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References