**New oral anticoagulants in the management of venous thromboembolism: A major advance?**

# New oral anticoagulants in the management of venous thromboembolism: a major advance?

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For the last 60 years, vitamin K antagonists (VKAs) have been the only available oral anticoagulant for the primary and secondary prevention of both arterial and venous thromboembolism. However, VKAs have unpredictable pharmacokinetics as well as complex food and drug interactions leading to variable anticoagulation, and the consequent need for relatively frequent, costly, and inconvenient blood testing to monitor the drug's activity. An industry of anticoagulant clinics in both primary and secondary care has grown up to cater for those requiring monitoring. Despite this, bleeding due to VKAs has remained a major cause of iatrogenic admission to hospital.1,2 One can also argue that a culture of fearfulness exists around patients receiving VKAs due to the complexity of managing these patients perioperatively, when they are ill, or receiving new medication. Moreover, in the current climate of concern about patient safety, in view of the poor safety record of VKAs, would such a drug be granted a license today? New oral anticoagulants (NOACs) have the potential to revolutionize the primary and secondary prevention of thrombosis, for they have predictable pharmokinetics and thus are given in fixed doses and do not require monitoring.3 Moreover, they have minimal interactions with drugs or diet. The prospect of a less rigid lifestyle than that required when taking VKAs and the freeing from anticoagulation monitoring has made NOACs very attractive to patients. In the current issue of European Journal of Vascular and Endovascular Surgery, Kakkos et al. present a systematic review and meta-analysis analysing the effectiveness and safety of NOACs compared with conventional treatment of warfarin for treatment and secondary prevention of venous thromboembolism (VTE). Pooling together data from 10 randomized controlled trials, with nearly 38,000 patients, the authors showed that in the six trials looking at treatment of acute symptomatic VTE, NOACs were equivalent in efficacy to conventional treatment with VKAs in reducing VTE recurrence. However, NOACs proved to be safer than conventional treatment because there was a significantly reduced bleeding risk. In fact, major bleeding rates fell from 1.73% with the use of VKA to 1.08% with the use of NOACs. NICE now recommend 3 months of anticoagulant treatment in those with acute provoked VTE,4 and other guidelines recommend 3e6 months; but the issue of how long to continue anticoagulation in those who have had unprovoked VTE remains unresolved, with the trend being to use warfarin long-term in the majority. Three secondary prevention trials in patients with unprovoked VTE after acute treatment compared NOAC with placebo. There was a 7.2% rate of recurrence in those receiving placebo versus 1.3% in those receiving a NOAC, at the price of an increase in non-significant bleeding but not major bleeding (4.3% vs. 1.8). Overall the authors concluded NOACs conferred a net clinical benefit when compared to VKAs. Not only are NOACs attractive as regards their net clinical benefit and convenience, but a NICE Single Technology Assessment5 and Lefebre et al.6 have evaluated the cost efficacy of rivaroxaban in the management and secondary prevention of VTE showing that rivaroxaban is more costeffective (lower drug costs, fewer hospitalized days, less bleeding) than conventional treatment of low-molecularweight (LMW) heparin and VKAs in the acute treatment of VTE. Although cost-efficacy is higher than VKAs in longterm secondary use, it is still within an acceptable limit, due to the lower bleed rates and lower intracranial haemorrhage rates than VKAs.7 At the time of writing, rivaroxaban and dabigatran are the only agents to be licensed in Europe for primary and secondary prevention of VTE, but it is expected that apixaban will gain a license shortly, swiftly followed by edoxaban. So while strong arguments of efficacy, safety, costefficacy, and patient convenience and experience for using NOACs in the acute management of VTE

now exist, there has been some reluctance to use them in many centres, with concerns related to the absence of a direct reversal agent. Antidotes are being fast tracked in development: a direct anti-Xa agent and a direct anti-dabigatran molecule are being trialled. But for now, unlike warfarin which can be reversed quickly by replacing the missing Factors II, VII, IX, and X by injection of prothrombin complex concentrates, there is no direct antidote. However, we need to remember that there is no reversing agent for LMW heparin and fondaparinux either, and yet these are widely used with fewer bleeding problems than VKAs. All the NOACs except dabigatran are direct anti-Xa agents and thus their mechanism of action is similar to LMW heparin and indeed both have similarly short half-lives. Conceptually and pragmatically it is helpful to consider that rivaroxaban, apixaban, and edoxaban are oral forms of LMW heparin. Currently supportive strategies are the mainstay of treatment of bleeding with both LMW heparins and NOACs, with discontinuation of the drug, mechanical compression, surgical haemostasis measures, and administration of transfusion support; and because the half-life of these agents is short, they will unlike warfarin disappear from the circulation quickly. Moreover, warfarin reversibility while conceptually attractive was not shown to improve outcomes in warfarin-related severe bleeding, such as intracranial haemorrhage, suggesting that anticoagulation reversal may not influence clinical outcomes if bleeding occurs.8 If all supportive measures fail, then what reversal agents are available to initiate haemostasis? The use of recombinant active factor VII has had inconsistent results in clinical settings and it is use is not clearly established.9 Dialysis can represent an option.10 However, because more than 90% of some NOACs (e.g. rivaroxaban) are bound to protein, it can be considered in selected cases only. More recently, prothrombin complex concentrates have been shown as potential antidote to reserve the effect of rivaroxaban and dabigatran.11 However, in reality, it is our experience, that very few patients using these drugs routinely require an antidote to reverse the anticoagulant effects. Balancing the risk of clotting and the risk of bleeding still weighs heavily on the minds of clinicians. Knowing that evidence exists to support their effectiveness and safety for treatment and secondary prevention of VTE will certainly tip the scale in the favour of NOACs in their battle against the “VKA culture”.

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