Which oral anticoagulant to use: Factor Xa inhibitor or thrombin inhibitor?

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SUMMARY
The Hokusai–VTE study was a randomized, double-blind, double-dummy, international multicentre clinical trial evaluating edoxaban in the treatment of venous thromboembolism (VTE). The study was designed to include all patients, even those with extensive disease. The duration of treatment varied from 3 to 12 months and patients were followed up to 12 months. Parenteral heparin therapy was followed by either warfarin or edoxaban. The dose of edoxaban was halved to 30 mg once daily in patients with renal dysfunction or low body weight (<60 kg).

The primary efficacy outcome was defined as the incidence of recurrent deep vein thrombosis (DVT) or non-fatal or fatal pulmonary embolism. Pre-specified secondary efficacy outcome included the primary efficacy outcome combined with death either from cardiovascular disease or from any cause. The safety outcome was defined as the incidence of major bleeding or clinically relevant non-major bleeding. The study was designed to test the hypothesis that edoxaban would not be inferior to warfarin with regard to the primary efficacy outcome. The primary efficacy outcome was analysed with the use of a Cox proportional hazards model with stratification factors as covariates. The time to clinically relevant bleeding during the on-treatment period was compared with the use of Cox proportional hazards model. Time to event curves was calculated using Kaplan–Meier analysis. Pre-specified subgroup analyses were performed according to the status of right ventricular dysfunction in patients with pulmonary embolism. Right ventricular dysfunction was defined according to the level of N-terminal pro-brain natriuretic peptide (NT-proBNP) and right ventricular dimension on computed tomographic scan in a random sample of 1002 patients.

A total of 8292 patients were enrolled at 439 centres in 37 countries. There was good adherence to treatment in the edoxaban group. The international normalized ratio (INR) was in the therapeutic range for 63.5% of time. Recurrent VTE occurred in 130 of 4118 patients (3.2%) in the edoxaban group and in 146 of 4122 patients (3.5%) in the warfarin group (hazard ratio with edoxaban 0.89; 95% CI 0.70–1.13; p=0.001 for non-inferiority). In the group of patients presenting with pulmonary embolism and evidence of right ventricular dysfunction, recurrent VTE occurred in 15 of 454 patients (3.3%) in the edoxaban group and in 30 of 484 patients (6.2%) in the warfarin group (hazard ratio 0.52; 95% CI 0.28–0.98). Similar results were obtained in patients with right ventricular dysfunction as assessed by computed tomography (hazard ratio 0.42; 95% CI 0.15–1.20). In the 30 mg dose edoxaban group, recurrent VTE occurred in 22 of 733 patients (3%) in the edoxaban group compared with 30 of 719 patients (4.2%) in the warfarin group (hazard ratio 0.73; 95% CI 0.42–1.26).

With regard to safety outcomes, major and non-major bleeding occurred in 349 of 4118 patients (8.5%) in the edoxaban group and in 423 of 4122 patients (10.3%) in the warfarin group (hazard ratio 0.81; 95% CI 0.71–0.94; p=0.004 for superiority). The difference in risk (edoxaban minus warfarin) was –1.8% (95% CI –3.04 to –0.53). Major bleeding occurred in 56 patients (1.4%) in the edoxaban group compared to 66 (1.6%) in the warfarin group (hazard ratio 0.84; 95% CI 0.59–1.21). In the 30 mg edoxaban group, bleeding occurred in 58 of 733 patients (7.9%) and in 92 of 719 patients (12.8%) in the warfarin group (hazard ratio 0.62; 95% CI 0.44–0.86). Major bleeding occurred in 11 patients (1.5%) in the edoxaban group and in 22 patients (3.1%) in the warfarin group (hazard ratio 0.50; 95% CI 0.24–1.03). The rate of death and adverse events were similar in the two groups.

COMMENT
There were 101 977 000 prescriptions dispensed for warfarin in the UK in 2012 (population 53.01 million, 2011 Census) at a cost to the National Health Service of £24 674 800 in prescription costs alone. At the same time, the market share for other new oral anticoagulants (OACs) such as rivaroxaban, apixaban and dabigatran was much less compared to that for warfarin. Warfarin continues to remain the most commonly used OAC in the UK.

The Hokusai–VTE investigators have studied yet another novel OAC, i.e. edoxaban, belonging to the family of factor Xa inhibitors in a well-designed large multicentre trial, and provided convincing evidence to support edoxaban—a factor Xa inhibitor. Edoxaban was non-inferior to warfarin in the prevention of recurrent VTE and there was no increase in major and non-major bleeding. The therapeutic efficacy and safety was maintained with reduction in the dose of edoxaban in the group with renal insufficiency and low body weight (<60 kg). The study was conducted at 439 centres in 37 countries; we do not have information about the performance and outcome of individual centres and assume that they were equally represented in the trial outcome. The quality control was rigorous as 63.5% of patients receiving warfarin were in the therapeutic range and adherence to edoxaban treatment was 80% or more in 99% of that group.

Although there are major advantages in having a single-drug approach for all treatment phases and thus avoiding traditional bridging of anticoagulation with heparin and OAC, the authors claim to have achieved better recruitment of a high proportion of patients with severe grade of VTE by adopting this approach. This study includes a high proportion of patients with right ventricular dysfunction due to pulmonary embolism; there was a reduction in VTE recurrences among patients with right ventricular dysfunction assessed by NT-proBNP and computed tomography.

Undoubtedly, the confidence in edoxaban has been well established in this trial and it is an addition to the group of new OACs competing for a market share. However, the Hokusai–VTE investigators missed an opportunity in obtaining a formal cost-effective analysis that could have facilitated in planning a switch from warfarin to newer OACs.
So, which OAC to use?
The mainstay of traditional anticoagulation involves bridging parenteral heparin therapy to a vitamin K antagonist such as warfarin. Newer OACs have a better pharmacokinetic and pharmacodynamic profile and are, therefore, best placed to simplify the entire approach to anticoagulation. These newer OACs can be prescribed in fixed dosage without the need for blood monitoring. Trials with apixaban and rivaroxaban have shown that the traditional bridging approach of parenteral heparin to OAC may be replaced by single agent throughout the treatment period.\(^2\)\(^3\) There is now a wealth of experience with the new OACs in different indications. There are over 15,000 patients, including this trial, who have been recruited in comparing the newer OACs with warfarin for the treatment of acute VTE.\(^2\)\(^4\) Similarly, extended use of dabigatran, rivaroxaban, apixaban and edoxaban have proved to be effective in reducing the recurrence rate of VTE with a good safety profile.\(^5\)\(^6\) Further evidence in support of the newer OACs compared to warfarin in patients with atrial fibrillation has been summarized in a meta-analysis of three studies including 44,563 patients.\(^7\) Patients taking the new OACs had a reduced risk of all-cause stroke and systemic embolism (relative risk 0.78; 95% CI 0.77–0.99), haemorrhagic stroke (RR 0.45; 95% CI 0.31–0.68), all-cause mortality (RR 0.88; 95% CI 0.82–0.95) and vascular mortality (RR 0.87; 95% CI 0.77–0.98). There was a lower risk of intracranial bleeding and a favourable safety profile.

Three of these newer OACs (including edoxaban) belong to the family of factor Xa inhibitors while dabigatran is presently the only direct thrombin inhibitor for clinical use.

All these trials have shown an almost identical therapeutic and safety profile and there appears to be very little difference between the various newer OACs. However, there are reasons to believe that targeting factor Xa is better than targeting thrombin.\(^8\) The concept of amplification within the coagulation cascade has suggested that inhibiting factor Xa may be more beneficial than thrombin inhibitors. From a molecular perspective, the activation of one molecule of factor Xa leads to the production of 1000 molecules of thrombin. Several studies have supported this notion by highlighting the need for less heparin to inhibit thrombosis prior to thrombin formation than following its production. There is a need for direct comparison between the two compounds for better understanding of their role in clinical practice.

Despite all the advantages of the new OACs there are still many unanswered questions such as lack of an antidote, anticoagulation monitoring in the presence of interacting drugs, approaches to treatment failure and finally the need for balancing the risk and benefit in a VTE trial.

REFERENCES

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