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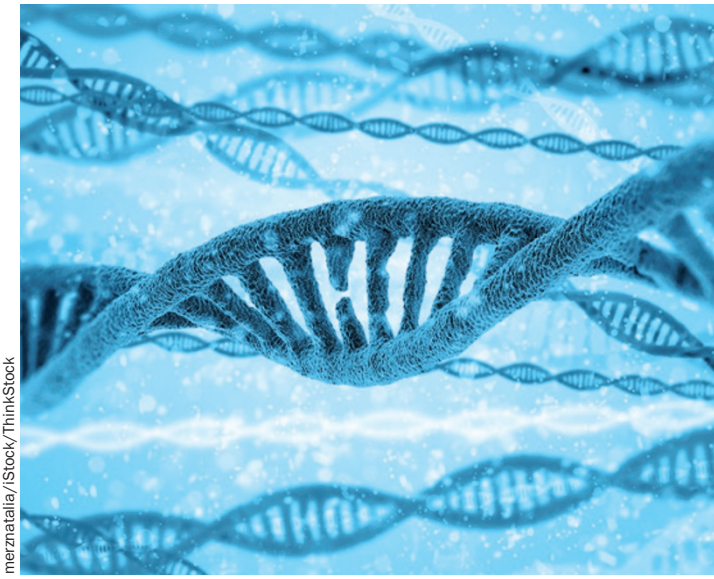
ANTICOAGULATION THERAPY

Optimal dosages and genotypes for edoxaban therapy



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Despite numerous trials demonstrating the favourable efficacy and safety profile of novel non-vitamin K antagonist oral anticoagulants compared with warfarin for the prevention of stroke in patients with atrial fibrillation (AF), concerns regarding their fixed dose regimen still remain. In addition, whether the presence of certain genetic variants can alter an individual's response to warfarin is unknown. These issues were explored in patients enrolled in the ENGAGE AF-TIMI 48 trial, and the results were presented at the 2015 ACC Scientific Sessions and published in the *Lancet*.

Altogether, 21,105 patients with AF participated in the ENGAGE AF-TIMI 48 study. Patients were randomly assigned to receive warfarin (dose adjusted according to an INR of 2.0–3.0), a high dose of edoxaban (60 mg once daily), or a low dose of edoxaban (30 mg once daily). Edoxaban dose was halved if certain pharmacokinetic factors that could increase drug exposure were present, including body weight ≤60 kg, a creatinine clearance range of 30–50 ml/min, or concomitant medication with potent P-glycoprotein interaction.

Ruff and colleagues sought to determine whether tailoring of the dose of edoxaban on the basis of clinical data prevented excess drug concentration and reduced bleeding risk. Patients who met the criteria for a dose reduction during the study had increased rates of stroke, bleeding, and death compared with those who did not. Although dose reduction lowered anti-activated factor Xa activity in both edoxoban groups, the efficacy of edoxoban was still comparable to warfarin. Both the high and low doses of edoxaban were associated with less bleeding than warfarin. Importantly, edoxaban dose reduction was associated with an even lower risk of bleeding. These findings provide further validation that dose optimization of edoxaban using clinical features alone can lower the risk of bleeding events.

In a separate study, Mega *et al.* assessed a subgroup of patients from the ENGAGE AF-TIMI 48 trial to determine whether certain genetic variants are associated with an increased risk of bleeding with warfarin use, and whether edoxaban can confer a greater safety benefit in these patients. Altogether, 14,348 patients were genotyped for variants in *CYP2C9* and *VKORC1*.

Among the 4,833 patients receiving warfarin, sensitive and highly sensitive responders, based on genotype, were more likely to experience over-anticoagulation compared with normal responders, and also had an increased risk of bleeding in their first 90 days of treatment. Notably, the lower bleeding risk associated with edoxaban versus warfarin use was more pronounced in the sensitive and highly sensitive groups than in normal responders during the first 90 days of treatment. These results demonstrate that patients with the *CYP2C9* and *VKORC1* variants derive a greater safety benefit from edoxaban compared with warfarin.

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Original articles Ruff, C. T. *et al.* Association between edoxaban dose, concentration, anti-Factor Xa activity, and outcomes: an analysis of data from the randomised, double-blind ENGAGE AF-TIMI 48 trial. *Lancet* doi:10.1016/S0140-6736(14)61943-7 | Mega, J. L. *et al.* Genetics and the clinical response to warfarin and edoxaban: findings from the randomised, double-blind ENGAGE AF-TIMI 48 trial. *Lancet* doi:10.1016/S0140-6736(14)61994-2