

Rivaroxaban to treat thrombotic antiphospholipid syndrome

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Thrombosis is one of the clinical hallmarks of antiphospholipid syndrome, a heterogeneous autoimmune disorder associated with the presence of antiphospholipid antibodies.¹ Thrombosis can occur in any vascular bed, but most patients present with venous thrombosis or ischaemic stroke.² Patients with antiphospholipid syndrome have a high risk of recurrent thrombotic events. The standard treatment for secondary prevention of venous thromboembolism is vitamin K antagonists. The intensity of anticoagulation needed to optimise prevention of secondary events has been debated, with arguments against and for high-intensity anticoagulation (international normalised ratio [INR] 3·0–4·0). Two randomised controlled trials showing that standard-intensity anticoagulation (target INR 2·0–3·0) is non-inferior to high-intensity treatment^{3,4} lessened the debate, but with the arrival of direct oral anticoagulants targeting either thrombin or activated coagulation factor X, the discussion has restarted.

The reported safety of direct oral anticoagulants combined with an increase in patients' wellbeing due to reduced need for monitoring are important arguments in favour of the use of these drugs for secondary prevention of venous thromboembolism. Case reports of patients with antiphospholipid syndrome who have had thrombosis while taking direct oral anticoagulants, however, have raised some concerns.^{5,6} Randomised controlled trials are urgently needed to resolve these issues.

In *The Lancet Haematology*, Hannah Cohen and colleagues⁷ provide evidence that similar anti-coagulation status can be achieved with rivaroxaban or warfarin in patients with antiphospholipid syndrome. They did a randomised controlled trial involving patients who were taking warfarin for previous venous thromboembolism, with a target INR of 2·5. After 6 months of follow-up during which anticoagulation status was assessed, only small differences in anticoagulation were found, leading the authors to conclude that rivaroxaban is non-inferior to warfarin.

The primary endpoint of the study was a laboratory comparison of the efficacy of warfarin and rivaroxaban. These two drugs have notably different effects on the coagulation system: warfarin essentially decreases the

concentrations of several coagulation factors, whereas rivaroxaban alters coagulation reaction kinetics by interfering with the prothrombinase complex. Thus the drugs cannot be compared directly for efficacy. For this reason, Cohen and colleagues compared anticoagulation intensity, assessed with calibrated automated thrombography, which is a holistic test of coagulation that measures thrombin generation rather than fibrin formation. Of note, though, the inherent differences between warfarin and rivaroxaban remain apparent in this assay, making it difficult to interpret the reported findings. The endogenous thrombin potential (the parameter most frequently reported in the literature for calibrated automated thrombography), indicated inferiority of rivaroxaban. By contrast, peak thrombin concentrations, which Cohen and colleagues argue more accurately reflects thrombotic risk than endogenous thrombin potential, suggested non-inferiority, supporting their conclusion of non-inferiority of rivaroxaban. Probably the most compelling evidence for the similar anticoagulant effects with rivaroxaban and warfarin was that the plasma concentrations of in-vivo markers of coagulation, thrombin-antithrombin complexes, D-dimers, and prothrombin fragment 1·2, were slightly raised in only a few patients in both treatment groups.

The most pressing question that needs to be answered in relation to the use of direct oral anticoagulants for prevention of venous secondary thrombosis in patients with antiphospholipid syndrome is whether rivaroxaban is non-inferior to warfarin and other vitamin K antagonists clinically as well as in the laboratory. With 54 patients in the rivaroxaban group and 56 patients in the warfarin group, the study by Cohen and colleagues⁷ did not have sufficient power to investigate the clinical efficacy of rivaroxaban. Nevertheless, no thrombotic recurrences or major bleeds were reported in the 6-month follow-up period, which suggests that this drug could be a safe and effective alternative for warfarin in a larger number of patients. Nevertheless, some caution should be applied because antiphospholipid syndrome is a highly heterogeneous disorder in terms of clinical presentation and risk profiles. Although Cohen and colleagues recruited a well defined, homogeneous group of patients, those



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with the high risk triple-positive phenotype (positive for lupus anticoagulant and antibodies against β_2 glycoprotein I and anticardiolipin⁸) were under-represented. Moreover, patients who had had recurrent venous thromboembolism while taking standard-intensity warfarin were excluded. Whether treatment with rivaroxaban would be equally efficacious in these subgroups of patients needs to be assessed.

Although the findings of Cohen and colleagues are hopeful,⁷ the efficacy of rivaroxaban treatment for secondary prevention of thrombosis in patients with antiphospholipid syndrome remains unclear. The outcomes of larger clinical trials investigating these questions are eagerly awaited.

Rolf T Urbanus

Department of Clinical Chemistry and Haematology, University Medical Centre Utrecht, 3584 CX Utrecht, Netherlands
R.T.Urbanus@umcutrecht.nl

I declare no competing interests.

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