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Rivaroxaban versus warfarin to treat patients with thrombotic antiphospholipid syndrome. Dr. Hannah Cohen about the results of the RAPS trial (Lancet Haematol 2016; 3: e426-36)

Because of the low frequency of clinical events, you selected a biological rather than a clinical outcome for this study. Why did you select this particular test?

The primary end point of the study was a laboratory comparison of the efficacy of warfarin and rivaroxaban because waiting for clinical events to occur would have required a substantially larger patient cohort with the study being conducted over several years. These two drugs have notably different effects on the coagulation system: warfarin essentially decreases the concentrations of several coagulation factors, whereas rivaroxaban, a direct factor Xa antagonist, alters coagulation reaction kinetics interfering with the prothrombinase complex. Thus the drugs cannot by compared directly for efficacy and the INR measurement does not reflect the anticoagulant intensity of rivaroxaban. We therefore compared anticoagulation intensity using calibrated automated thrombography, a global test of coagulation that measures thrombin generation rather than fibrin formation, and thereby allows assessment of the anticoagulant effects of warfarin and rivaroxaban despite these drugs' different modes of action.

Your study did not show non-inferiority of rivaroxaban compared with warfarin in reaching this particular outcome in APS patients having had a non-recurrent episode of venous thromboembolism. Yet, overall anticoagulation profile was similar in both groups, and no thrombotic event was observed. Will your finding translate into a change in clinical practice? What are the next steps?

The thrombin generation curve is quantified in terms of the lag time, time to peak thrombin generation, peak thrombin generation, and endogenous thrombin potential (ETP), which is the area under the curve. Warfarin affects all thrombin generation parameters equally, whereas rivaroxaban mainly affects the initiation and propagation phases of thrombin generation. Formation of the prothrombinase complex is delayed and lag time and time to peak thrombin generation are prolonged and, therefore, the ETP is greater than would be expected for the degree of anticoagulation.

When anticoagulation intensity was assessed by percentage change in ETP alone, rivaroxaban was inferior to warfarin in patients with APS and previous venous thromboembolism. However, peak thrombin generation was lower with rivaroxaban and, therefore, the overall thrombogram indicated no difference in thrombotic risk. This conclusion is supported by in-vivo coagulation activation marker concentrations being raised in only a few patients in both treatment groups. Additionally, no new thrombotic events were seen during 6 months of treatment, there were no major bleeding episodes and quality of life was significantly better in the rivaroxaban group than in the warfarin group.

We concluded from our results that rivaroxaban seems to offer an effective, safe and convenient alternative to warfarin in APS patients with previous venous thromboembolism requiring standard intensity anticoagulation. RAPS can therefore be regarded to be a game-changer in the treatment of this APS subgroup.

The next steps are further studies to define the role of rivaroxaban and other direct oral anticoagulants in APS patients, including those with venous thromboembolism who need higher intensity anticoagulation (i.e. those with recurrent venous thromboembolism while taking standard intensity anticoagulation) or APS patients with stroke or other arterial thrombosis.

What about patients with APS and arterial thrombotic events? Is there a place for new anticoagulation strategies in such patients?

Stroke is the second most common cause of death worldwide and the most important cause of adult disability. About 20% of patients with stroke have APS. There is a pressing need to define optimal antithrombotic treatment, in particular the role of rivaroxaban and other direct oral anticoagulants, in APS patients with stroke or other arterial thrombosis. We aim to undertake a study of rivaroxaban versus warfarin to establish the clinical utility of rivaroxaban in APS stroke patients.

Interview conducted between Dr. Hannah Cohen, Consultant and Honorary Reader in Haematology, University College London Hospitals NHS Foundation Trust and University College London, and Professor Bernard Lauwerys, Rheumatology Unit, Université catholique de Louvain, Belgium.

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