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Predictors of clinically relevant bleeding during extended anticoagulation for cancer-associated venous thromboembolism (API-CAT): a post-hoc analysis of a randomised, non-inferiority trial

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Abstract

Background: Extended anticoagulation with reduced-dose apixaban was shown to be non-inferior to full-dose apixaban for preventing recurrent venous thromboembolism (VTE) in patients with active cancer and to be associated with fewer clinically relevant bleeding complications in a non-inferiority trial. In this post-hoc analysis, we sought to identify predictors associated with clinically relevant bleeding.

Methods: API-CAT was a randomised, double-blind, non-inferiority trial done in 121 hospitals in 11 countries. Eligible patients were adults older than 18 years, with active cancer diagnosed histologically (other than basal-cell or squamous-cell carcinoma of the skin, primary brain tumour, or intra-cerebral metastasis) and acute proximal deep-vein thrombosis or pulmonary embolism, 6 months or more of completed anticoagulation, and an Eastern Cooperative Oncology Group performance status of 0-2. Patients were centrally randomly assigned (1:1) to apixaban 5·0 mg or 2·5 mg twice daily orally for 12 months using an interactive web-response system, and stratified by trial centre, index event, and cancer site. The primary endpoint, reported previously, was the centrally adjudicated fatal or non-fatal recurrent venous thromboembolism. The primary objective for this post-hoc analysis was to identify predictors of clinically relevant bleeding during extended therapy in the overall population and to evaluate how these predictors vary according to cancer type. The post hoc-analysis was done in the intention-to-treat population, multivariable competing-risks regression model was built with clinically relevant bleeding as the dependent variable and was adjusted for apixaban dose. The association between potential predictors and clinically relevant bleeding was expressed as subdistribution hazard ratio (HR) with 95% CIs. Variables with a p value less than 0·05 were considered statistically significant associated with clinically relevant bleeding. The trial is registered with ClinicalTrials.gov (NCT03692065) and is complete.

Findings: Between Oct 11, 2018, and Sept 6, 2023, 1766 patients were randomly assigned to the reduced-dose group (n=866) or the full-dose group (n=900). Median follow-up was 12·9 months (IQR 11·8-13·2). 766 (43·4%) of 1766 patients were male and 1000 (56·6%) were female. At 12 months, clinically relevant bleeding occurred in 238 patients. In the overall population, anaemia and/or

thrombocytopenia (subdistribution HR 1·93 [95% CI 1·27-2·95]), age 75 years or older (1·51 [1·14-2·02]), pulmonary embolism as the index event (1·47 [1·03-2·10]), and male sex (1·38 [1·05-1·82]) were significantly associated with an increased risk of clinically relevant bleeding. These results are homogeneous across cancer sites, with no evidence of statistically significant interaction between dose regimen and any predictor (all $p_{interaction}$>0·30).

Interpretation: During extended treatment for cancer-associated VTE, four predictors of clinically relevant bleeding were identified in the overall population, with no evidence of interaction with the dosing regimen. Although the API-CAT study was not designed to specifically address anticoagulation discontinuation, our findings might help clinicians to more effectively balance the benefits and risks of extended anticoagulant therapy.

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