RESEARCH LETTER

Rivaroxaban concentration in patients with deep vein thrombosis who reported thrombus progression or minor hemorrhagic complications: first Polish experience

Introduction Rivaroxaban, a direct factor Xa inhibitor, is approved for the prevention of stroke and systemic embolism in nonvalvular atrial fibrillation as well as for the prevention and treatment of deep vein thrombosis (DVT) and pulmonary embolism.[1-4] In addition, rivaroxaban is currently accepted in combination with antiplatelet agents for the prevention of atherothrombotic events in patients with acute coronary syndromes. Rivaroxaban has predictable pharmacokinetics and pharmacodynamics and, in clinical practice, it is used at fixed doses without the need for routine coagulation monitoring. However, rivaroxaban is contraindicated in patients with creatinine clearance of less than 30 ml/min. The peak plasma level is reached within 2 to 4 hours, and the half-life is between 7 and 11 hours in patients with normal renal and hepatic function.[1,2]

Rivaroxaban can prolong prothrombin time (PT, with a subsequent increase in a calculated international normalized ratio [INR]) and activated partial thromboplastin time (aPTT), with weak associations of these parameters with plasma concentrations of the drug,[5-7] measured directly by noncoagulation tests such as high-performance liquid chromatography–tandem mass spectrometry.[8]

Monitoring of rivaroxaban concentrations may be useful in certain clinical situations such as urgent surgery, thromboembolic or bleeding complications, or suspicion of an overdose.[8-10] The most commonly used assay for this purpose is a modified antifactor-Xa assay. We investigated rivaroxaban concentrations in DVT patients who reported on-treatment thrombosis progression or minor hemorrhagic complications.

Patients and methods We studied 23 patients (8 men and 15 women), aged 44 ±15 years, who received rivaroxaban (20 mg/d) following DVT within previous 1 to 6 months prior to blood collection. Patients were diagnosed with DVT progression, defined as a symptomatic increase of the thrombus size on ultrasound scan, following at least 28 days of rivaroxaban therapy and up to 7 days from the onset of the thrombosis signs and symptoms (n = 11). The other patient group represented subjects who reported persistent minor hemorrhagic complications, including easy bruising or oral or nasal cavity bleeding while on rivaroxaban despite a negative personal or family history of a tendency for bleeding (n = 12).

The exclusion criteria were any acute illness, cancer, severe heart failure, creatinine clearance of less than 30 ml/min, impaired liver function (transaminases >2 × upper limit of normal), concomitant medications interfering with the anticoagulant effect of rivaroxaban, eg, amiodarone. All patients declared abstaining from the use of nonsteroidal anti-inflammatory agents, including aspirin, within the preceding month.

Blood was drawn between 9 and 11 AM on an outpatient basis, 2 to 28 hours since the last dose of rivaroxaban. Hemoglobin, creatinine, PT, INR, and aPTT were determined by routine laboratory techniques. Rivaroxaban concentration was measured by the anti-Xa chromogenic assay, Biophen DiXaI (Hyphen Biomed, Neuilly-sur-Oise, France) according to the manufacturer's instructions.

Twenty apparently healthy subjects not receiving rivaroxaban matched for age, sex, and renal function served as controls. In 13 controls, the results of the anti-Xa chromogenic assay were negative, while in 7 individuals measurable levels were in the range of 1 to 23 μg/l.

All subjects gave informed consent to participate in the study. The study complied with the World Medical Association Declaration of Helsinki regarding ethical conduct of research involving human subjects.

Statistical analyses were performed with the SPSS 20.0 software. The Mann–Whitney test was used to compare differences between patients on rivaroxaban and controls, whereas the Kruskal–Wallis test, followed by a test for multiple

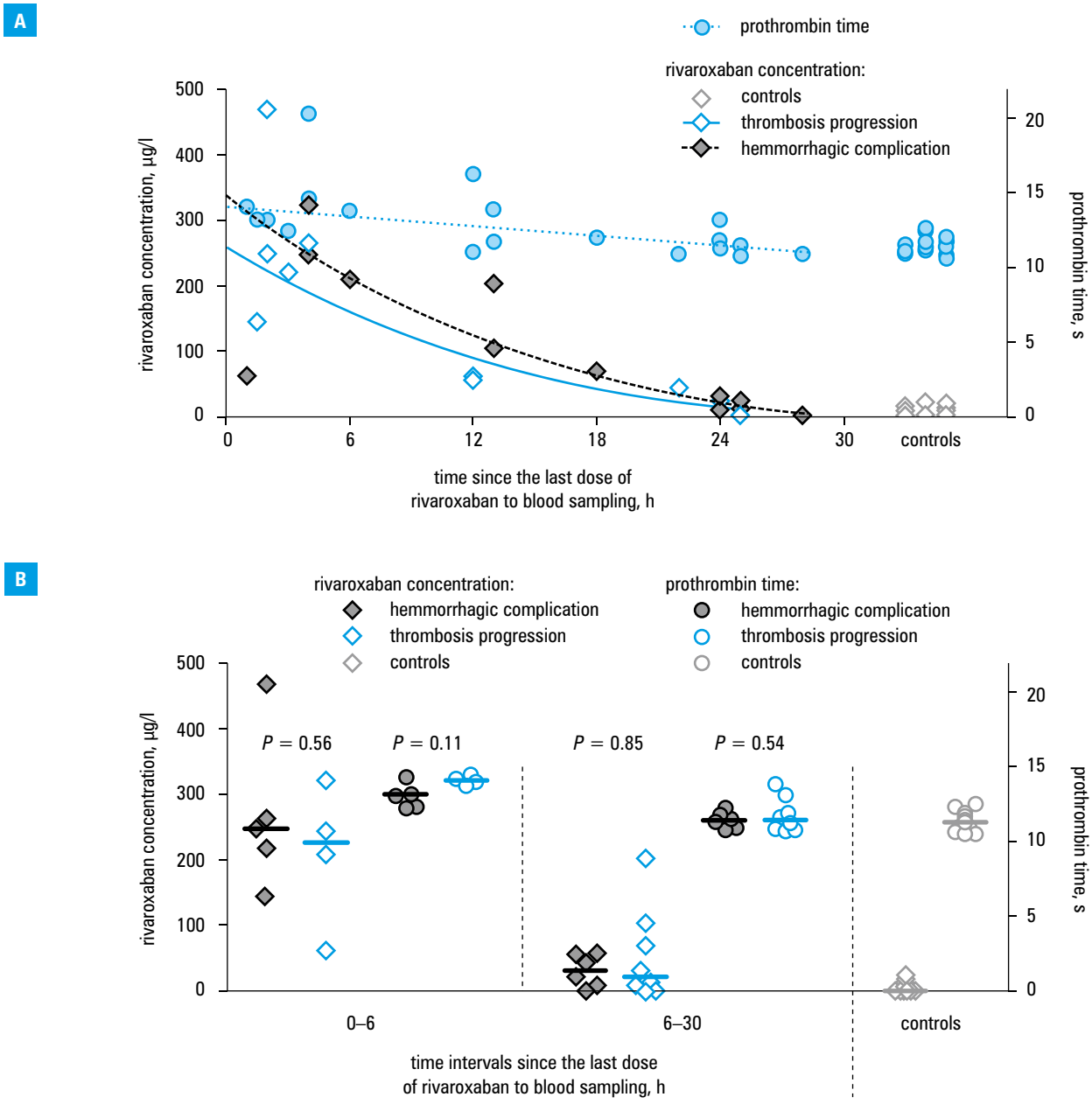

FIGURE Rivaroxaban concentration and prothrombin time in relation to the time (**A**) and time intervals (**B**) since the last dose of rivaroxaban to blood sampling

comparisons of mean ranks, was used to compare differences of single measurements in the 3 groups. The association between 2 variables was assessed by the Spearman test. A multiple regression analysis was applied to determine independent predictors of rivaroxaban concentrations. The analysis of covariance assuming homogeneity of slopes including age, sex, renal function, and time since the last rivaroxaban dose to blood sampling as covariates was used to compare rivaroxaban concentrations between patients with thrombus progression and minor bleeding complications. A 2-sided $P < 0.05$ was considered statistically significant.

Results aPTT tended to be longer (median, 28.9 vs. 27.1 s, $P = 0.10$) and PT was longer (12.3 vs. 11.4 s, $P = 0.035$) in patients on rivaroxaban compared with controls, which corresponded with the calculated INR values (1.09 vs. 1.0, $P = 0.002$, respectively).

Patients with a history of thrombus progression or hemorrhagic complications did not differ with regard to age, sex, renal function, aPTT, PT, INR, and drug concentrations. A univariate analysis showed that the rivaroxaban concentration was associated only with the time since the last rivaroxaban dose to blood sampling ($R^2 = 0.63$; $P < 0.001$) and was correlated with PT both in patients with thrombosis progression ($R^2 = 0.76$; P=0.01) as well as in those with minor hemorrhagic complications ($R^2 = 0.84$; $P < 0.001$) (FIGURE 1A).

The pharmacokinetic curves of the relationship between the rivaroxaban concentration and the time since the last rivaroxaban dose and blood sampling overlapped in the 2 compared groups (FIGURE 1A). Between the 2 groups of thrombosis progression or minor hemorrhagic complications, rivaroxaban concentrations and prothrombin time did not differ significantly in the subgroups classified on the basis of the time since the last rivaroxaban dose to blood sampling (FIGURE 1B).

The time since the last rivaroxaban dose to blood sampling was the only independent predictor of the rivaroxaban concentration (R^2 = 0.72; P <0.0001). By the analysis of covariance, after adjustment for age, sex, renal function, and time to sampling there was no difference in rivaroxaban concentrations between DVT patients with thrombus progression and those with minor hemorrhagic complications (F = 0.34, df = 1, P = 0.59).

Discussion The current study describes the first Polish experience with the measurements of rivaroxaban concentrations in everyday practice. We observed that, in DVT patients, plasma rivaroxaban concentrations estimated using the anti-Xa assay did not differ between patients who reported thrombus progression or minor hemorrhagic complications, who were maintained on rivaroxaban therapy. Our results suggest that the association between thrombotic or bleeding events and insufficient or markedly elevated plasma rivaroxaban concentrations might not be obvious. One may speculate that poor compliance is crucial for the anticoagulant effects of rivaroxaban, while easy bruising and other mucocutaneous bleedings reported by many older patients on anticoagulation (which do not lead to drug withdrawal) are commonly unrelated to the accumulation of rivaroxaban. We confirmed that the time since the last dose of the drug to blood sampling is a major determinant of the plasma rivaroxaban concentration.[4-6] It should be highlighted that the self-reported bleeding complications observed during treatment with rivaroxaban might be associated with the use of the out-of-counter anti-inflammatory medications with antiplatelet actions, who were not reported by patients.

We confirmed that plasma rivaroxaban concentrations are associated with PT. However, PT does not allow to quantitatively assess the anticoagulant effect of rivaroxaban.[8-10] Moreover, our findings indicate that the measurements of rivaroxaban concentrations are of limited value in everyday practice and should be performed only under specific clinical circumstances, eg, in patients with severe bleeding or requiring urgent invasive treatment.[8-10]

In conclusion, we found that plasma rivaroxaban concentrations in patients with DVT may not be helpful in discriminating subjects who developed thrombosis progression or minor hemorrhagic complications on rivaroxaban. Patients with a history of such complications and measurements of rivaroxaban levels should be evaluated with caution given the lack of the therapeutic range for the results of the anti-Xa assay in subjects receiving this anticoagulant. The measurable levels of rivaroxaban detected in a few control subjects deserve consideration suggesting that anti-Xa assays could show falsely elevated levels of the drug and standardization of those assays is urgently needed. Moreover, additional factors other than high levels of rivaroxaban that may lead to thrombotic or bleeding events should be identified.

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Conflict of interest The authors declare no conflict of interest.

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