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Full Length Article

Impact of gender on safety and efficacy of Rivaroxaban in adolescents & young adults with venous thromboembolism

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ABSTRACT

Background: The objective of the present study was to evaluate safety and efficacy of Rivaroxaban (RIVA) being administered as a routine medication for patients with venous thromboembolism (VTE) in a multicenter outpatient cohort.
Methods: 212 consecutively admitted outpatients (14–<55 years) with VTE treated with standard RIVA were recruited between January 2013 and December 2015. Monitoring of RIVA trough levels along with anti-factor-Xa-activities, factor (F) VIII, Ristocetin-cofactor and von Willebrand factor antigen were performed. Safety endpoints were defined as significant bleeding requiring any medical intervention such as: dose reduction, withdrawal of RIVA or death related to therapy. Efficacy endpoints were defined as any re-VTE or thrombus progression during treatment.
Findings: Patients were followed over a median period of 16 months. The bleeding incidence rate per 100 patient-years was 17.8% in fertile/premenopausal women and 4.0% in men with an annualized re-VTE rate of 0.48% (women only). The median daily RIVA dose of 0.25 mg/kg in females was significantly higher compared to males with 0.21 mg/kg ($p < 0.0001$), clearly correlated to FXa-activities. In bleeders compared to non-bleeders median RIVA dose per kg/body weight was significantly higher (0.26 mg vs. 0.22 mg; $p = 0.008$). Multivariate analysis adjusted for gender, body mass index, RIVA dose and FVIII revealed an increased hazard of 3.4% in women to develop RIVA-induced bleeding. Additionally, a gradual decrease of FVIII per IU/ml was significantly associated with clinical relevant bleeding.
Interpretation: Our data demonstrated a high incidence of mucosal type bleeding in women on standard RIVA. This has clinical implications suggesting a need for RIVA monitoring in selected individuals that are at an increased bleeding risk.
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1. Introduction

Venous thromboembolism (VTE) includes deep vein thrombosis and pulmonary embolism (PE) and is associated with significant morbidity and mortality [1]. Recommendations for antithrombotic therapy suggests treating patients with acute VTE for at least 3 to 6 months with an option to continue anticoagulation in patients with ongoing risk factors and in subjects with unprovoked VTE. This recommendation assumes that the major bleeding risk does not exceed the benefit of recurrence-free survival [2]. Until recently, vitamin K antagonists (VKA) were the only available oral anticoagulants. However, apart from its effectiveness VKA therapy in acute VTE is complicated mainly by the significant variations in metabolism as well as drug and food interactions,

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necessitating routine monitoring of the anticoagulant intensity [3]. The latter is important to ensure the delicate balance between prevention of recurrence and the incidence of major bleeding complications.

Among other indications, direct oral anticoagulants (DOACs) have been developed for the treatment of VTE to offer efficient anticoagulation while eliminating the need for monitoring. The four main DOACs currently being approved for VTE treatment in adults are the direct factor Xa inhibitors Apixaban, Edoxaban and Rivaroxaban (RIVA) and the direct thrombin-inhibitor Dabigatran. Compared with VKA preparations, mainly warfarin or phenprocoumon, DOACs as a group of medications show comparable efficacy with a significant lower bleeding risk in patients with VTE [4,5]. Furthermore, different from VKA, DOACs offer a rapid onset of action as well a short offset period [6]. Apart from a similar efficacy rate a recently published systematic review comparing Apixaban, Dabigatran, Edoxaban and RIVA demonstrated that the bleeding risk among DOACs was not identical. Hemorrhagic complications were reported significantly less frequently with Apixaban compared to the remaining DOACs, and with Dabigatran compared to Edoxaban and RIVA, respectively [7].

For the selective factor Xa inhibitor RIVA large phase 3 trials in VTE and PE have demonstrated a high efficacy and safety profile [8,9]. Comparable to VKA treatment bleeding is the most common adverse effect of RIVA. The bleeding pattern may also vary with respect to female gender [10], especially in younger VTE patients, which was shown recently in an UK report [11].

Since real-world outpatients with VTE may differ not only with respect to age, gender distribution or comorbidities from subjects enrolled in phase 3 VTE trials, the objective of the present non-industry-sponsored study was to evaluate efficacy and safety of standard RIVA administered as a routine medication in a multicenter cohort of male and fertile/premenopausal female patients aged 14 to <55 years with VTE.

2. Methods

2.1. Ethics

The present multicenter cohort study was performed in accordance with the ethical standards laid down in the updated version of the 1964 Declaration of Helsinki and was approved by the medical ethics committee of the University of Münster, Germany. Written informed consent was provided in all cases (patient; patient & parents in adolescent cases) prior to study participation.

2.2. Study Population and Study Design

From January 2013 to December 2015, 265 consecutively admitted adolescents and adults with newly diagnosed VTE were enrolled in the study. During the study period three patients (one adolescent) refused to be included in this study.

2.3. Inclusion and Exclusion Criteria

Inclusion criteria for VTE cases were the following: (i) age older or equal to 14 years (puberty status > or equal Tanner 3) and <55 years at time of VTE diagnosis; and *(ii)* objective confirmation of VTE by standard radiologic imaging methods, including compression sonography, venography, computed tomography [CT] venography, or magnetic resonance [MR] venography for VTE, and spiral CT angiography or lung perfusion scintigraphy for pulmonary embolism. Exclusion criteria consisted of: *(i)* lack of consent to participate, *(ii)* loss to follow-up, *(iii)* concomitant aspirin or clopidogrel administration [12], *(iv)* antiphospholipid syndrome, and (*v*) malignancy or cardiac diseases. In addition, menopausal women and women who underwent hysterectomy or endometrial ablation prior start of RIVA treatment were excluded.

2.4. Clinical Procedures

Diagnosis of VTE in patients was confirmed by hematologists specializing in VTE diseases. All patients with VTE underwent baseline evaluation at enrollment by history and physical exam to evaluate evidence of existing VTE, and were seen subsequently at least every three to six months. All reports of interim VTE were confirmed by review of the medical records, including radiographic imaging studies. Clinical data collection included patient demographics and disease characteristics, clinical risk factors for VTE, laboratory test results, RIVA therapy regimens and outcomes. Duration of RIVA therapy was prescribed according to updated antithrombotic therapy guidelines from the American College of Chest Physicians [2]. The current dosage recommendation of RIVA for all patients was 15 mg twice daily at VTE onset followed by once daily 20 mg after 3 weeks. Bleeding events were classified as "minor" or "major" using the International Society on Thrombosis and Haemostasis (ISTH) classification [13]. Menorrhagia and abnormal uterine hemorrhage was assessed by using a pictorial blood assessment card (PBAC) [14]. Furthermore, criteria for abnormal uterine bleeding included: menstrual bleeding duration > 8 days, inter-menstrual bleeding, menstrual blood loss causing anemia or requiring unscheduled contact with a gynecologist or resulted in any medical (change of anticoagulant regimen, use of tranexamic acid, iron supplementation) or surgical intervention [15].

Recurrent VTE was confirmed by experienced radiologists using imaging performed in cases of clinically suspected new events demonstrating fresh thrombotic material within the lumen of the veins (i.e. a new intraluminal filling defect compared with the previous radiologic imaging studies).

2.5. Outcome Parameters

Primary study objective: composite safety endpoints were defined as significant bleeding episodes, minor or major, requiring any medical intervention such as RIVA dose reduction or withdrawal of RIVA or death related to bleeding. Efficacy endpoints were defined as any VTE, thrombus progression during treatment or VTE-related death. Secondary study objective included time elapsed from the beginning of treatment to bleeding. This latter was evaluated by the probability of bleeding-free survival (BFS). On an explorative basis a generic standardized health-related quality of life (HrQoL) questionnaire was performed [16].

2.6. Laboratory Methods

Using the BCS-XP instrument (Siemens, Marburg, Germany), plasma-based clotting factor analyses were performed using reagents from Siemens (Marburg, Germany) and Haemochrom Diagnostica (Essen, Germany) as per manufacturer instructions. Standard laboratory techniques were used to investigate factor FVIII activity, Ristocetin-cofactor activity (RICO), von-Willebrand-factor antigen (VWF:Ag), RIVA trough (24 h) and peak levels (Coamatic LMWH, non antithrombin-supplemented Xa-based assay; chromogenic substrate S-2732; Haemochrom Diagnostica, Essen, Germany) along with anti-factor-Xa-activities (Coamatic LMWH, non-antithrombin-supplemented Xa-based assay, Haemochrom Diagnostica, Essen, Germany). In detail, a five-point RIVA calibrator set purchased from Technoview (Technoclone, Vienna, Austria) was used to measure RIVA drug concentrations between 0 and 170 ng/ml. Plasma samples above 170 ng/ml were increasingly diluted so that the drug concentration of at least two patient dilutions lied within the range covered by the calibration curve. Validation experiments with an in-house patient plasma pool showed an intra-assay coefficient with variation of 1.78% at concentrations of 70 ng/ml. In a similar manner, a five-point LMWH calibrator set purchased from Technoview (Technoclone, Vienna, Austria) was used to measure *anti*-factor-Xa-activities between 0.0 IU/ml and