The role of pharmacogenetics as a possible risk factor for rivaroxaban – associated bleeding

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KEYWORDS: rivaroxaban, side effects, bleeding, pharmacogenetics.

CITATION: Cardiol Croat. 2022;17(9-10):278. | https://doi.org/10.15836/ccar2022.278

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Introduction: Rivaroxaban has large interindividual trough concentration variability affecting its efficacy and safety. This variability could be associated with age, liver and kidney function, concomitant illness and therapy[1]. Rivaroxaban is a substrate of ABCB1 and ABCG2 drug transporters[2], and CYP2J2, CYP3A4/5 metabolic enzymes. The polymorphisms of these genes may affect the pharmacokinetics and consequently safety profile of rivaroxaban. *Aim:* To evaluate possible risk factors for rivaroxaban-associated bleeding in patients treated for cardiovascular diseases.

Patients and Methods: Presented data are part of the larger ongoing prospective case-control study "Pharmacogenomics in Prediction of Cardiovascular Drugs Adverse Reaction" (funded by the Croatian Science Foundation) with 402 patients recruited by now. Clinical and laboratory data were collected. Pharmacogenetic analyses were performed using specific TaqMan® DME and SNP Assays on 7500 Real-Time PCR System for genotyping of CYP3A4*1B, *22, CYP3A5*3, CYP2J2*7, ABCB1 (c.1236C>T, c.3435C>T), and ABCG2 (c.421C>A) gene variants. For drug-drug interactions (DDI), The Lexicomp® Clinical Decision Support System was applied.

Results: Sixteen patients (median age 73 years; rivaroxaban median dose 17.5 mg) with rivaroxaban-associated bleeding: gastrointestinal (N=9), epistaxis (N=5), haematuria (N=1) and gynaecological (N=1) were analysed. In 9/16 DDI with increased bleeding risk were found. Two patients were CYP3A4*22 carriers (*1/*22 and *22/*22), three were CYP3A5*3 heterozygous, four were CYP2J2*7 heterozygous, two patients had ABCB1 T/T+T/T genotype, four ABCG2 C/A and one A/A genotype. Three patients who experienced bleeding did not have any of investigated risk factors.

Conclusion: Our data suggest a possible role of clinical and pharmacogenetic factors and their interactions in predicting rivaroxaban-associated bleeding, but further comprehensive research is warranted.

RECEIVED:
October 27, 2022
ACCEPTED:
November 10, 2022

LITERATURE

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