Summary

Background: Warfarin is the most commonly used Vitamin K antagonist worldwide for treatment and prevention of arterial and venous thromboembolic events. Its use is limited by low therapeutic index and significant interindividual variability in daily dose. The individual genetic profile explains the majority of warfarin dose response variability. Carriers of variant alleles *2 and *3 in CYP2C9 gene and low dose haplotype A/A in gene VKORC1 have significantly lower dose of warfarin resulting in higher risk of overcoagulation with higher risk of major bleeding complications. Due to its low therapeutic index and significant influence of individual genotype on clinical outcomes is warfarin ideal for pharmacogenetic testing.

Aim: To assess clinical utility of warfarin pharmacogenetic warfarin dosing algorithm in routine clinical practice and to evaluate an association between CYP2C9 and VKORC1 variant genotype and the occurrence of major bleeding complications in a warfarin-treated cohort.

Methods: Detailed clinical data were acquired from consenting study subjects with known and stable warfarin daily dose. All participants were genotyped for variant polymorphisms in genes CYP2C9 and VKORC1 using HRM analysis. Accuracy of prediction was assessed in cohort of 280 subjects. Own algorithm was developed based on derivation cohort (n = 175) and subsequently validated in validation cohort (n = 223). For risk estimation of major bleeding complications was collected cohort of patients with major bleeding while on the warfarin therapy (n = 51) and its control group (n = 143).

Results: The highest accuracy in predicting warfarin daily dose in our cohort of Czech patients had algorithm by Sconce et al (coefficient of determination, R^2 = 58,4%), other compared algorithms had significantly lower accuracy (by Anderson R^2 = 21,9% and by Gage R^2 = 23,8%). Algorithm developed by our group had good accuracy in validation cohort with coefficient of determination 62,3% - higher then previously published algorithms in general and also in our validation cohort (Sconce 55,3%). Regarding bleeding risk according individual genotype we proved higher risk in carriers of at least one variant allele in gene CYP2C9. Patients who are carriers of 3 variant alleles of the genes CYP2C9 and VKORC1 exhibited a significantly higher risk of major bleeding events during the initiation and also the maintenance phases of warfarin therapy. On the other hand we observed a significantly lower risk of bleeding in carriers of CYP2C9 wild type genotype (*1/*1).

Conclusion: Warfarin pharmacogenetics has a potential thanks to its accuracy in predicting daily dose of warfarin in routine clinical practice of specialized anticoagulation clinics. Vigilant and careful management of patients with a higher variant allele count or CYP2C9 variant homozygotes, including switching to newer anticoagulants, could be considered in this high-risk cohort. Warfarin with usage of pharmacogenetic testing is still an effective and safe alternative to new oral anticoagulants.