REVERSE-HYBRIDIZATION-BASED GENETIC TESTING FOR THE PREDICTION OF ANTICOAGULANT DOSE REQUIREMENT

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Background *Coumarin derivatives (as warfarin or phenprocoumon) are the most widespread oral anticoagulant drugs for the prevention and treatment of arterial and venous thromboembolic disorders. However, these vitamin K antagonists have a narrow therapeutic range and a wide interindividual variability in dose requirement. Despite adjustment for clinical variables adverse events (delay in achieving a stable maintenance dose or bleeding complications) are frequently encountered during the initial phase of therapy. Genetic polymorphisms in the drug-targeted vitamin K epoxide reductase complex 1 (VKORC1) and in the drug metabolizing enzyme CYP2C9 have been reported to account for the majority of variations in the therapeutic response to warfarin.*

Results *We developed a genetic test (StripAssay) for the detection of -1639G > A and 3730G > A in the VKORC1 gene, and 430C > T and 1075A > C in the CYP2C9 gene. The test is based on multiplex PCR, followed by reverse-hybridization of biotin-labeled amplification products to a parallel array of allele-specific oligonucleotides immobilized on membrane teststrips. Genotyping for VKORC1 polymorphisms and the functionally defective CYP2C9 variants *2 and *3 allowed the classification of patients into high, intermediate and low dose responders to phenprocoumon (Marcumar™), the most commonly used oral anticoagulant in Central and North European countries. A rapid DNA extraction protocol, ready-to-use reagents and teststrips, and the potential for automation of the hybridization/detection step, make the StripAssay convenient and easy to perform within < 6 hours.*

Conclusion *A simple and reliable diagnostic tool was developed and evaluated for predicting the response of patients to phenprocoumon treatment. The results obtained in our study will assist clinicians to achieve a more individualized anticoagulant therapy.*