Influence of *CYP2C9, VKORC1,* and *CYP4F2* polymorphisms on the pharmacodynamic parameters of warfarin: A cross-sectional study.

Background:

Warfarin is the most common drug evaluated in pharmacogenetic-guided dosing studies. However, gaps remain related to the influence of genetic polymorphisms of *CYP2C9*, *VKORC1*, and *CYP4F2* on the specific pharmacodynamic parameters such as warfarin sensitive index (WSI), prothrombin time international normalized ratio (PT-INR) variability, Warfarin composite measures (WCM), and health related quality of life (HrQoL).

Methods:

A cross-sectional study was conducted in non-smoking adults receiving warfarin for at least six months. *CYP2C9* (rs1057910 and rs1799853), *CYP4F2* (rs2108622), and *VKORC1* (rs9923231) polymorphisms were assessed using real-time polymerase chain reaction. Anticoagulation control as defined by National Institute of Health and Clinical care Excellence guidelines, time spent in therapeutic range, stable warfarin dose, WSI, log-INR variability, WCM, documented bleeding episodes, and HrQoL were the outcomes.

Results:

Two-hundred and thirty-six patients were recruited. Seventy-five (31.8%) had polymorphisms in *CYP2C9*, 143 (60.6%) had at least one T allele in *CYP4F2*, and 133 (56.4%) in *VKORC1*. Presence of T alleles in *CYP4F2* and *VKORC1* were observed with

poor anticoagulation control. The stable warfarin doses decreased with the presence of either *2 or *3 in *CYP2C9* akin to the presence of T alleles in *VKORC1* but increased with T alleles in *CYP4F2*. Individuals with either *2 or *3 or both in *CYP2C9* and T alleles in *VKORC1* had a greater WSI. Similarly, *VKORC1* polymorphisms was associated with a greater INR variability. Presence of T alleles in *CYP4F2* was observed with lower WCM scores. No significant differences in the HrQoL were observed between the genotypes. A lower risk of bleeding was observed in individuals without T alleles in *CYP4F2*. Presence of T alleles in *CYP4F2* in groups II and III *CYP2C9* and *VKORC1* genotypes was associated with reduced TTR and poor anticoagulation control. Groups II and III *CYP2C9* and *VKORC1* genotypes were observed with reduced stable warfarin dose, increased WSI, higher log-INR variability, and increased bleeding risk.

Conclusion:

The evaluated genetic polymorphisms significantly influenced all the pharmacodynamic parameters of warfarin. Genetic evaluation of *CYP2C9*, *VKORC1*, and *CYP4F2* polymorphisms prior to initiating warfarin may assist in achieving a better optimal therapeutic response.