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Methods for Improving Warfarin Dosing

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Background: Warfarin is an inexpensive and highly effective anticoagulant that inhibits the synthesis of vitamin K dependant clotting enzymes. Warfarin is used for the prophylaxis and/or treatment of thromboembolic complications from atrial fibrillation, cardiac valve replacement, orthopedic, and peripheral vascular surgery and to reduce the risk of death after myocardial infarction. Effective dosing occurs within a narrow therapeutic range that varies between individuals and results in one of the highest adverse reaction rates of any drug. Standard initiation therapy at most institutions is empirically based, starting for most patients at 5 mg/day. It is likely that improvements in warfarin dosing regimens will be realized using mathematical models that incorporate individual phenotypic, genetic, and environmental factors to allow personalized dosing of warfarin.

Methods: We developed a multivariate mathematical model to predict the initial warfarin dose. Both phenotypic and genetic data were incorporated into the model. Phenotypic data included age, gender, body surface area, concomitant medications, treatment indication, and co-morbidities. DNA was tested for polymorphisms in CYP2C9, VKORC1, gamma carboxylase, factor VII, and apolipoprotein E (Apo E).

Results: Our model explained 55% of the variability in stable warfarin dose. The model included clinical factors and CYP2C9 and VKORC1 polymorphisms. Polymorphisms in gamma carboxylase, factor VII, and Apo E did not significantly add to the model.

Conclusions: Warfarin dosing based on mathematical models incorporating both phenotypic and genetic elements has substantial potential to improve patient safety early in therapy when the risks of adverse health events are especially high. Previously, we conducted a pilot study demonstrating the ability to genotype patients for CYP2C9 and predict their starting dose using our model. This pilot study was the first to apply real-time genetic testing prior to warfarin dosing. Larger studies should now be done to determine if models that include genetic testing at CYP2C9 and VKORC1 in conjunction with clinical factors reduce warfarin-related adverse events in a cost-effective manner. Through collaborations in the HMO network it will be possible to expand these studies to additional ethnic groups and to collect data regarding bleeding events and personalized coumadin dosing in the future.