Disclaimer:
This document is intended to provide the user with information on available evidence and existing recommendations as to the use of pharmacogenetic (PG) testing to guide warfarin dosing. At this time, it is not the intent of the AC Forum or the Centers of Excellence (COE) to take a position for or against PG-guided warfarin dosing. Anticoagulation management services are encouraged to use this information to determine if PG-guided warfarin dosing may a viable additional method of anticoagulation management for their individual practice and/or facility.

Background:
An area of significant interest regarding optimizing warfarin’s efficacy and safety is pharmacogenomic (PG) testing for polymorphisms that affect a patient’s warfarin requirements. Evidence suggests that as much as fifty percent of the variability in warfarin dosing requirements can be explained when these polymorphisms are considered along with clinical characteristics of the patient. (1) Several warfarin PG algorithms have been validated, and some researchers suggest this method may be superior to standard clinical algorithms. (2-6).

To date the largest barriers to routinely using PG information include cost, availability, and lack of adequate scientific data supporting the reduction of hard endpoints such as ischemic events and bleeding.(1,7-11)

Existing recommendations:

Proponent
In 2011, the Clinical Pharmacogenetics Implementation Consortium (CPIC) of the National Institutes of Health Pharmacogenomics Research Network published a guideline intended to “assist in the interpretation and use of CYP2C9 and VKORC1 geno-type data for estimating therapeutic warfarin dose to achieve an INR of 2–3, should genotype results be available to the clinician.” (1)

Within that guideline, they state “The published evidence strongly supports our level A (strong) recommendation that, if genetic information is available, warfarin dosing should be estimated using a pharmacogenetic dosing algorithm, but in the absence of access to such an algorithm, a genotype dosing table is superior to other approaches that ignore genetic information in predicting stable warfarin dose.”

The United States Food and Drug Administration (FDA) revised the warfarin labeling in 2010 to include dosing recommendations based on CYP2C9 and VKORC1 genotypes (12).

Opponent
In the most recent iteration of its guidelines, the American College of Chest Physicians (ACCP) state “There are four RCTs of pharmacogenetic testing-based dosing vs. standard dosing; all addressed warfarin initiation. (4, 6, 13-14) The studies included patients with artificial heart valves, atrial fibrillation, or acute VTE. All studies were small (total n =544). None showed any difference in thrombotic events, major bleeding, or survival”.

Based on the lack of information regarding clinical outcomes, the ACCP provides the following Grade 1B recommendation: “For patients initiating VKA therapy, we recommend against the routine use of pharmacogenetic testing for guiding doses of VKA.”

Emerging evidence:
While there are limited prospective data from randomized trials on the use of genetic information to guide warfarin dosing, and the impact on clinical outcomes is unknown, more recent and ongoing studies may provide additional guidance on this topic. (15-18). Antithrombosis providers are encouraged to stay abreast of evidence emerging from these clinical trials.

Potential evolution in antithrombosis management:
Interest in the area of PG testing and personalized medicine will continue to grow and utilization of PG testing may become more routine. If so, antithrombosis providers may need to consider developing criteria to identify patients who warrant PG testing, such as patients being initiated on warfarin therapy, those with apparent warfarin resistance or severe INR lability and/or those deemed at high risk of bleeding. Such criteria would need to be reviewed and updated longitudinally. A multidisciplinary practice collaborative between the reference laboratory, providers and the antithrombosis management service would be optimal to ensure appropriate testing, interpretation, documentation and application of PG results.
Provisions of use:
There are some matters that should be taken into consideration with currently available validated PG dosing algorithms. These algorithms are likely most beneficial to patients newly initiated on warfarin therapy. Patients who have been on stable, long-term warfarin therapy will be less likely to derive any benefit from this approach. There is little to no data regarding algorithm-based dosing of warfarin in pediatric patients, thus recommendations for using PG warfarin dosing in non-adult populations do not currently exist. Additionally, derivation cohorts have consisted predominantly of European Caucasians, and the results may not be applicable to other ethnic groups. However, there is a growing body of information regarding use in other populations, such as Hispanics and African Americans (19,20). Finally, PG dosing algorithms should always be used in conjunction with other clinical patient information (e.g., nutrition status, bowel function, concomitant disease states) that may not be captured within a particular algorithm.

Resources:
A freely available PG dosing algorithm is available at [www.warfarindosing.com](http://www.warfarindosing.com). It allows the user to input individual patient clinical characteristics with or without the patient’s genetic information.

The University of Illinois Hospital and Health Sciences System-Chicago has a multidisciplinary Pharmacogenetics Consult Service. Their practice guidelines and procedures may be found within the pharmacogenetic section of the Disease State Management pillar on the Centers of Excellence website.

References: