Clinical Chemistry Trainee Council
Pearls of Laboratory Medicine
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TITLE: Warfarin Pharmacogenetics

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Slide 1: Title slide

Slide 2:
Warfarin is a commonly prescribed anticoagulant used in the prevention and treatment of thromboembolic disorders. Warfarin is widely prescribed and from the time period of 1998–2004, the U.S. saw a 45% increase in warfarin prescriptions. With the aging population and increased projected prevalence of atrial fibrillation, the number of warfarin prescriptions is predicted to continue to increase.

Slide 3:
There are many challenges in regulating warfarin dosing. Traditionally, warfarin efficacy is evaluated via the prothrombin time. To be efficacious and safe, the INR for individuals on warfarin must be maintained in a narrow therapeutic window. Typically, the INR during warfarin treatment should optimally fall between 2 and 3 for most patients, although the target INR may vary depending on indication for treatment. Once the INR rises above the therapeutic window, the patient is susceptible to major bleeding complications, especially for INR values greater than or equal to 4. If the INR falls below the therapeutic window, this indicates that the individual is not receiving effective warfarin therapy and is at risk for thrombotic complications. Bleeding and thrombotic complications are most likely to occur within the first few weeks of initiation of warfarin treatment.

Slide 4:
Amongst prescribed medicines, warfarin is the most commonly implicated medication in U.S. Emergency Department visits. When this information was published in 2007, there were approximately 177,500 E.D. visits for adverse drug events annually, with warfarin-related ED visits contributing to approximately 30,000 of those events. From the time period of 1993 to 2005, and based on data from the FDA's Adverse Event Reporting System, warfarin–associated cases had rates of 86% for bleeding with serious outcome and 10% for fatal bleeding. Compared to other drugs, warfarin has a high frequency of adverse events, with a high frequency of serious and fatal outcomes.

Slide 5:
Regulating warfarin dosing can require multiple titrations to achieve a stable, target INR. As shown here, most individuals require about 5mg of warfarin per day. However, a significant percent of individuals require lower doses or higher doses of warfarin. Lower doses, as shown on the left side of the graph, are associated with warfarin sensitivity, whereas higher doses of warfarin are associated with warfarin resistance. Genetically, we understand more about warfarin sensitivity than warfarin resistance.

Slide 6:
This pie graph shows the contribution of different factors to warfarin dosing variability. Approximately 30-35% of warfarin dosing variability is due to genetic variation, especially variation in the VKORC1 and CYP2C9 genes. Other factors contributing to warfarin dosing variability include weight, age, drugs, diet, co-morbidities, smoking status, and other unknown factors.

Slide 7:
Here you can see that CYP2C9 and VKORC1 are involved in pharmacokinetic and pharmacodynamic processes of warfarin response, respectively. Pharmacokinetics has been touted as "what the body does to the drug" whereas pharmacodynamics is "what the drug does to the body". The left side of the figure depicts the pharmacokinetic processes and shows that warfarin is given as a racemic mixture of R- and S-warfarin. S-warfarin is the more potent form of warfarin and is mainly metabolized by hydroxylation by the cytochrome P450 2C9, or CYP2C9, enzyme.

The right side of the figure depicts the pharmacodynamic processes and shows that the main target of both R- and S-warfarin is Vitamin K epoxide reductase or VKOR. VKOR is encoded for by the VKORC1 gene. Inhibition of VKOR by warfarin results in keeping Vitamin K-dependent clotting factors in the inactive state.

Slide 8:
As mentioned in an earlier slide, CYP2C9 and VKORC1 are the two main genes known to be involved in warfarin dosing variability. CYP2C9 has two common alleles that lead to decreased enzymatic activity, known as *2 and *3. Both of these alleles are characterized by amino acid missense changes.
VKORC1 has a single nucleotide polymorphism in the promoter region of the gene that results in a decrease in promoter activity, leading to decreased production of the VKOR protein.

Because of the relatively high contribution of genetics to warfarin dosing variability, the FDA relabeled warfarin in August 2007 to recommend PGx testing of CYP2C9 for warfarin therapy. A second label update was issued in January 2010, whereby the label was updated to include the effects of VKORC1 as well as provide PGx-guided dosing ranges.

Slide 9:
The allele frequencies of the common alleles in CYP2C9 and VKORC1 are depicted here. You can see that they are fairly common across the Caucasian population. The VKORC1 promoter polymorphism is believed to contribute to the majority of warfarin sensitivity in the Asian population. Other alleles in addition to CYP2C9 *2 and *3 are present in the African-American population, but at this time they are not routinely measured in some laboratories.

Slide 10:
As mentioned earlier, the FDA updated the warfarin label in 2007 and 2010 to provide caution related to warfarin sensitivity. In 2010, they included a table, shown here, which provides genetic-guided dosing ranges. Across the top is the CYP2C9 genotype, with *1 being wild-type or normal. Along the left side of the table is the VKORC1 genotype. You can see that individuals with a combination of genotypes leading to warfarin sensitivity, as depicted in the right side of the table, will be expected to require lower doses of warfarin.

Slide 11:
There are many technology options for genotyping in the clinical laboratory. However, only a handful of tests had been 510K-cleared for pharmacogenetic testing related to warfarin therapy. These are listed here and include the Nanosphere Verigene platform, approved in September 2007; the Autogenomics INFINITI platform, approved in January 2008; The ParagonDx Gentris RT-PCR platform, approved in May 2008; the Osmetech eSensor platform, approved in July 2008; and the TrimGen eQ-PCR LightCycler platform, approved in February 2009.

Slide 12:
Many different agencies and groups have produced differing guidelines and recommendations for warfarin PGx testing. In 2008, the American College of Medical Genetics provided their support for warfarin PGx testing, if performed within the first 3 days of prescribing and prior to initiation of therapy in orthopedic patients. Also in 2008, the College of American Pathologists stated that they believe there is ample evidence to support warfarin PGx testing at least for some patients. But, in that same year, two other organizations, the American College of Chest Physicians and the American Society of Hematology, did not lend their support to warfarin PGx testing until randomized clinical trial data was available that indicated the benefits of such testing. In August 2009, the Centers for Medicare and Medicaid Services announced that Medicare would not reimburse warfarin PGx testing except in the setting of randomized control trials. In 2010, the National Academy of Clinical Biochemistry submitted their statement endorsing warfarin PGx testing. Thus, considerable variability for guidelines and recommendations exists among professional organizations and government agencies.

Slide 13:

In 2010, the results of the large Medco-Mayo Warfarin Effectiveness Study were published. This study evaluated hospitalization rates in patients beginning warfarin therapy with genotyping vs historical controls who did not have genotyping. What this study found was that patients whose warfarin dosing was guided by genotyping had 31% fewer hospitalizations for any reason and hospital admissions for thromboembolism or bleeding were 28% less frequent in the genotyped group. Therefore, the results of this study support warfarin PGx testing from a clinical outcomes standpoint.

Slide 14:

In summary, polymorphisms in CYP2C9 and VKORC1 account for most of the interindividual genetic variability in warfarin dosing. There are a handful of FDA 510K cleared tests available for warfarin PGx testing. Warfarin dosing tables and algorithms based on genotype and other factors are also available. As far as guidelines and recommendations for warfarin PGx testing by professional organizations and government agencies, there is considerable variability amongst these groups. However, prospective, randomized control trials could be helpful in answering some of the remaining questions regarding warfarin PGx testing utility.