Pharmacogenetics of warfarin

* Warfarin, first introduced in the 1950s
* now become the most commonly prescribed oral anticoagulant for the prevention of thromboembolism in patients with deep vein thrombosis, atrial fibrillation or prosthetic heart valve replacement
* Warfarin exists as a racemic mixture of (R) and (S)—enantiomers with the (S) form being more potent than the (R) isomer.
* Even though warfarin is highly efficacious, it is plagued by a narrow therapeutic window, and large interindividual variations in the warfarin dosage required for achieving optimal anticoagulation
* Variations can range as much as 10–20 fold differences in the dose required to achieve optimal anticoagulation.
* significant ethnic dose differences, Asian populations usually require lower doses relative to Caucasian or African populations
* Because of the large difference in the dose required for warfarin, the anticoagulation effect must to be monitored regularly

GENETIC FACTORS INFLUENCING WARFARIN RESPONSE

1. Initial focus was on the warfarin-metabolizing enzyme cytochrome P450 2C9 (CYP2C9), which metabolizes the potent (S) warfarin.2
2. It was soon identified that polymorphisms in CYP2C9 were associated with reduced warfarin dose requirement.
3. The most common allele is CYP2C9\*1, which is considered as the wild-type allele
4. The most common variant in European ancestry are:

* CYP2C9\*2 (rs1799853), which has an Arg144Cys substitution( absent in some Asian)
* CYP2C9\*3 (rs1057920), which has an Ile359Thr substitution

1. The minor allele of these two variants produces a metabolically impaired enzyme with activities reduced by 30% (CYP2C9\*2) and 80% (CYP2C9\*3
2. These individuals are also at greater risk of bleeding during warfarin treatment and require longer time to achieve stable target INR
3. (CYP2C9\*5, \*6, \*8 and \*11) are also identified
4. second major genetic determinant, vitamin K epoxide reductase subunit 1 (VKORC1), was identified
5. VKORC1 is responsible for the regeneration of vitamin K epoxide to vitamin K and is the rate-limiting step in the vitamin K regeneration
6. The most commonly used VKORC1 variant is a noncoding variant (VKORC1 1639 G4A, rs9923231) which lies in the promoter region of VKORC1
7. The 1639 G allele destroys a transcriptionbinding site (E-box) that resulted in increased promoter activity
8. individuals that carry the G allele require higher warfarin doses than those with the A allele
9. This association was soon confirmed in three major populations (African, Asian and Caucasian)