Review

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Oral anticoagulation: a critique of recent advances and controversies

Munir Pirmohamed[1,2], Farhad Kamali[3], Ann K. Daly[3], and Mia Wadelius[4]

[1] The University of Liverpool, Liverpool L69 3BX, UK
[2] Royal Liverpool and Broadgreen University Hospital National Health Service (NHS) Trust, Prescot Street, Liverpool L7 8XP, UK
[3] Newcastle University, Newcastle upon Tyne NE2 4HH, UK
[4] Uppsala University, 751 85 Uppsala, Sweden

There have recently been significant advances in the field of oral anticoagulation, but these have also led to many controversies. Warfarin is still the commonest drug used for clotting disorders but its use is complicated owing to wide inter-individual variability in dose requirement and its narrow therapeutic index. Warfarin dose requirement can be influenced by both genetic and environmental factors. Two recent randomized controlled trials (RCTs) came to different conclusion regarding the utility of genotype-guided dosing; we critically explore the reasons for the differences. The new generation of oral anticoagulants have been demonstrated to be as efficacious as warfarin, but further work is needed to evaluate their safety in real clinical settings.

Oral anticoagulation

Anticoagulation is now established as an important treatment modality for several acute and chronic conditions characterized by the occurrence of, or tendency to, thromboembolism. Acutely, many patients can be treated with parenteral anticoagulants, most commonly subcutaneous low molecular weight heparin. For long-term treatment, however, oral anticoagulants are needed. The vitamin K antagonists (warfarin, phenprocoumon, acenocoumarol, and phenindione) have remained the mainstay of oral therapy for many decades, but their dominance is now being challenged by the new oral anticoagulants (dabigatran, rivaroxaban, apixaban, and edoxaban). This review focuses on the role of the vitamin K antagonists (in particular warfarin) in the treatment of thromboembolic disorders, highlighting the controversy associated with the use of genotype-guided dosing. We also discuss the choice created by the availability of the new oral anticoagulants, highlighting some of the most recent findings.

Pharmacology of warfarin

Warfarin has now been in use for over 60 years, and remains the most commonly prescribed oral anticoagulant worldwide. Warfarin is used by over 1% of the UK population [1], and in the USA there are over 30 million prescriptions annually. Warfarin inhibits the recycling of vitamin K in the coagulation cascade and thereby prevents the activation of clotting factors II, VII, IX, and X, as well as proteins C, S, and Z [2]. There are many advantages to the use of warfarin (Table 1), but also many factors that make it difficult to predict the clinical response to the drug. Warfarin remains one of the commonest drugs implicated in adverse drug reactions causing hospital admission [3]. Bleeding is a major complication of warfarin therapy, the risk of which increases proportionately with the intensity of anticoagulation as indicated by the international normalized ratio (INR) value [4]. For example, in an elderly population, the risk of bleeding was over 25-fold higher at INR >4.1 compared with an INR between 2.0–3.0. The percentage time in therapeutic range (TTR) is a widely accepted measure of patient anticoagulation control and treatment safety; TTR has been shown to be a predictor of major hemorrhage, ischemic stroke, and all-cause mortality [5].

Safety concerns about warfarin lead to drug discontinuation in about 25% of patients in the first year, particularly in the elderly [4]. Many different approaches have been deployed to improve anticoagulation control in patients on warfarin therapy including the deployment of specialized anticoagulation clinics for routine monitoring, the introduction of computerized dosing software programs and dosing algorithms to improve the accuracy of dosing, and the introduction of education programs to improve patient adherence with therapy [6]. However, these measures have been variably implemented in clinical practice. Patient self-monitoring of INR has also been trialed; this is effective in some patients who can be appropriately trained in the independent use of a hand-held INR monitoring device. However, a meta-analysis showed that self-monitoring results in only a modest, non-significant improvement in TTR [7], despite a higher number of INR measurements annually [8]. Patient self-management (where patients are responsible for both their INR measurement and warfarin dosing) has been shown to be no more cost-effective than specialized anticoagulation clinics [9].

Inter-individual variability in response to warfarin

There is wide inter-individual variability in clinical response to warfarin. Many clinical and patient factors can affect the response to warfarin (Figure 1). Age is perhaps the best characterized of these, with elderly patients generally being more sensitive to warfarin. This

Corresponding author: Pirmohamed, M. (munirp@liverpool.ac.uk).
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Table 1. Advantages and disadvantages of using warfarin

Advantages	Disadvantages
Clinical familiarity with use	Variability in dose requirement and response
Well-studied clinical pharmacology	Need for regular monitoring
Cost	Drug interactions
Readily available biomarker (INR)	Interactions with food
Availability of antidotes	Interactions with alcohol

is thought to be related to the decrease in liver mass in the elderly resulting in their lower capacity to eliminate warfarin and reduced production of clotting proteins [10]. It is important to note that most of the factors that influence sensitivity to warfarin are not accounted for in dosing regimens, except for age, for which some guidelines suggest a more cautious approach in older patients (usually over 65 years of age, but cut-offs vary) particularly at the time of warfarin initiation [11].

There has been a great deal of interest in genetic determinants of inter-individual variability in response to warfarin. Warfarin is administered as a 50:50 mixture of R- and S-enantiomers, with S-warfarin being 3–5-fold pharmacologically more potent than R-warfarin [2]. S-warfarin is metabolized by the cytochrome P450 isoform CYP2C9. The *CYP2C9* gene is highly polymorphic and a large number of polymorphisms have been described (http://www.imm.ki.se/CYPalleles/cyp2c9.htm) which vary considerably in frequency with ethnicity (discussed below). The variants *CYP2C9*2* and *CYP2C9*3* are the best-characterized, reducing enzyme activity to 12% and 5% in the homozygous state, respectively, compared to the wild type genotype (*CYP2C9*1/*1*) [12,13]. Consistent with the reduction in enzymatic activity, patients carrying these variant alleles require lower warfarin doses. A systematic review showed that carriage of *CYP2C9*2* leads to a reduction in warfarin dose by about 1 mg/day, while *CYP2C9*3* carriage leads to reduction in dose by about 1.6 mg/day [14].

Vitamin K epoxide reductase complex 1 (*VKORC1*) is the major genetic determinant of warfarin dose requirement [15], reflecting its central role in the mechanism of action of warfarin. The G–1639A polymorphism has been the most widely genotyped, and is in complete linkage disequilibrium with several other single-nucleotide polymorphisms (SNPs) [16]. The minor alleles are associated with lower warfarin dose requirement, with the *VKORC1* −1639 AA genotype (rs9923231) being associated with a dose reduction of up to 3 mg/day [14]. The functional basis is thought to be related to a decrease in transcriptional activity [17]. Rare mutations in *VKORC1* have also been associated with resistance to warfarin [18].

Cytochrome P450 4F2 (CYP4F2) has also been shown to affect warfarin dose requirements [16]. The *CYP4F2* V433 M variant (rs2108622) increases dose requirements because of reduced liver enzyme levels, reduced vitamin K metabolism, and thus the need for higher warfarin dose requirements to inhibit VKORC1 [19]. Several variants in other candidate genes have been investigated but with mixed results [2,16], and will not be considered further.

The studies conducted to date have evaluated the effect of genetic polymorphisms on several clinical outcome measures, most commonly stable doses. However, a great deal of heterogeneity has been observed in the definitions used – for example, for stable dose, 34 different definitions have been used across 55 studies [14]. Despite this, the association of stable warfarin dose with *CYP2C9*, *VKORC1*, and *CYP4F2* SNPs has been confirmed in three genome-wide association studies (GWAS) [20–22], with *VKORC1* contributing the most and *CYP4F2* the least (Figure 1).

The genetics of warfarin-related bleeding events has also been investigated, but most studies had inadequate statistical power. Two systematic reviews have shown that the carriage of the *CYP2C9*3* allele seems to increase the risk of warfarin-related bleeding [14,23]. Interestingly, a recent study has suggested that the risk of lobar cerebral hemorrhage in patients on warfarin is increased in apolipoprotein E (*APOE*) *ε2* and *ε4* carriers, but there was no interaction between APOE and warfarin [24]. Further studies will be necessary to elucidate whether there are independent genetic risk factors for intracerebral hemorrhage associated with warfarin, which is perhaps the most feared complication given that it can lead to life-long disability.

Warfarin-dosing algorithms

The association between *VKORC1* and *CYP2C9* genetic polymorphisms and warfarin dose requirement is one of the most highly replicated genotype–phenotype associations, its relevance having been shown in a large number of ethnic groups. This has spurred the development of several dosing algorithms which incorporate age, body mass index (or body surface area), interacting medications, and *CYP2C9* and *VKORC1* as genetic factors. Other algorithms have also incorporated *CYP4F2* as well as clinical factors. The International Warfarin Pharmacogenetics Consortium (IWPC), a collaboration of 21 research groups from nine countries on four continents, developed algorithms using data from 4043 patients, which were validated in 1009 subjects [25]. The IWPC showed that a pharmacogenetic-based warfarin dosing algorithm (incorporating *CYP2C9* and *VKORC1* genetic polymorphisms) was more accurate in predicting stable maintenance dose compared

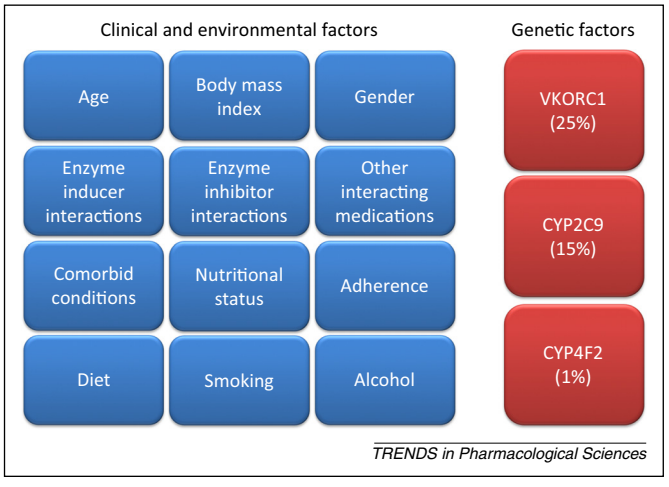

Figure 1. Determinants of response to warfarin.