

Editorial Focus

Pharmacogenomics of coumarin anticoagulants: Are we underestimating the role of *CYP2C9*?

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More than 60 years after its successful introduction for the prevention of thromboembolic events, the coumarin anticoagulant warfarin is still one of the most frequently prescribed cardiovascular drugs. The recently conducted Active W study once again established its therapeutic superiority over even a combination of antiplatelet drugs for the prevention of stroke in patients suffering from atrial fibrillation, the most common indication for coumarins (1).

However, despite its undisputable therapeutic benefits, coumarins are notorious for the difficulties which are found in establishing and maintaining an adequate dose, reflecting the inter-individual and intra-individual variability in dose requirements and necessitating frequent monitoring of the International Normalized Ratio (INR). This variability is a consequence of age, of genetic factors and of environmental factors such as compliance, variations in vitamin K intake, several disease states and drug interactions. The main genetic research targets are the *CYP2C9* gene, encoding the main metabolizing enzyme of coumarins, and the *VKORC1* gene, encoding the target protein for coumarins on Vitamin K epoxide. Since the pioneering study by Aital et al. (2) who reported a higher bleeding risk and lower dose requirements in warfarin users carrying a *CYP2C9**2 or *3 allele in a British population, many studies have examined the effect of *CYP2C9* variant alleles on the anticoagulant status of the different coumarins (3). Since 2004 the scope of pharmacogenetic studies in users of coumarins has been broadened by the identification of the *VKORC1* gene (4), and by the finding in several studies that polymorphisms of the *VKORC1* gene contributed considerably more to the variability in warfarin dose requirements than polymorphisms of the *CYP2C9* gene (5, 6). This finding raised new expectations about enhancing the safety of warfarin therapy by genotype-guided dosing.

In this issue of *Thrombosis and Haemostasis* Meckley et al. add a valuable contribution to the pharmacogenetic research area of coumarin anticoagulants (7). They evaluated the relative effects of *VKORC1* and *CYP2C9* genotypes on several relevant patient outcomes, such as time to therapeutic range, bleeding events and overanticoagulation, in a European-American cohort

of warfarin patients. Their finding that the *VKORC1* genotype explains a larger part of the inter-individual variability in warfarin dose requirements than the *CYP2C9* genotype (27% and 12%, respectively) is in agreement with most other studies (3). However, for the clinically more relevant outcomes bleeding, overanticoagulation and time to stable anticoagulation, Meckley et al. found a strong association with the *CYP2C9* variant status, whereas the *VKORC1* variant status was only significantly associated with overanticoagulation in the first month of warfarin therapy.

In two studies among users of the coumarins acenocoumarol and phenprocoumon similar results have been reported (8, 9). For both coumarins, the *VKORC1* genotype explained a considerably larger part of the variability in dose requirements than the *CYP2C9* genotype, whereas the time to stable anticoagulation was associated only with the *CYP2C9* genotype: with the *CYP2C9**3 allele in users of acenocoumarol and, perhaps somewhat surprisingly, with the *CYP2C9**2 allele in users of phenprocoumon. In these studies the risk of overanticoagulation was strongly increased in patients with variant alleles of both *CYP2C9* and *VKORC1* compared to patients with no variant alleles or a variant allele of either *CYP2C9* or *VKORC1*. More importantly, in a prospective follow up study among African-American and European-American warfarin users, Limdi et al. (10) found an increased risk of major bleeding in patients with a variant *CYP2C9* genotype in both populations compared to patients with the *CYP2C9* wild type, whereas no such association was found with the *VKORC1* 1173 C/T genotype. This bleeding risk was more strongly increased before stabilisation on warfarin, but a significant association of major bleeding risk with the *CYP2C9* genotype persisted thereafter.

Although some studies failed to find an association between the *CYP2C9* genotype and time to stable anticoagulation in users of warfarin (11, 12), these studies also failed to report such an association with the *VKORC1* genotype. So, the majority of the hitherto performed studies and the study of Meckley et al. (7) in this issue, strongly suggest an association of the *CYP2C9* variant status with the clinically relevant outcomes bleeding and time to

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stable anticoagulation. No such association has been demonstrated for the *VKORC1* variant status despite the larger contribution of the latter to the variability in coumarin dose requirements. This gives rise to some reflection on the consequences of knowledge of the *CYP2C9* genotype in users of coumarin anticoagulants.

Meckley et al. (7) explain the slower stabilisation and increased bleeding risk in patients with a *CYP2C9* variant allele by the decreased warfarin half-life compared with wild-type patients and they give some suggestions for better warfarin dose adjustments in *CYP2C9* variant patients. However, it is doubtful whether only a decreased half-life as such can explain the apparent difficulties in dose-finding. It is also conceivable that the decreased metabolic capacity makes *CYP2C9* variant patients more sensitive to environmental factors such as comedication-like *CYP2C9* substrates, which might interfere more with the metabolism of coumarins than in patients with full *CYP2C9* capacity- and comorbidities (like heart failure or infectious diseases), contributing to more fluctuations in coumarin response and making the effect of the *CYP2C9* variant status even more unpredictable.

Whatever the explanation might be, the retarded stabilisation reported by Meckley et al. and the increased bleeding risk even after stabilisation according to the study of Limdi et al. (10) strongly suggest that the *CYP2C9* variant status is associated with an increased intra-individual variability compared with the *CYP2C9* wild-type status, irrespective of *VKORC1* genotype. It will be a major challenge to incorporate this knowledge into dose algorithms and to improve the intra-individual fine-tuning of dose adjustments in patients with *CYP2C9* variant alleles. This

might be an even greater challenge than the incorporation of *VKORC1* genotypes to assess the inter-individual differences in coumarin dose requirements which manifest earlier in therapy.

In August 2007 the Food and Drug Administration (FDA) changed the labelling of warfarin by incorporating information about the effects of genetic variants of *CYP2C9* and *VKORC1* on warfarin response and by suggesting lower initiation dosages in patients with genetic variations in *CYP2C9* and *VKORC1*. However, translation of this genetic information into more reliable dose algorithms is still far away. In a randomized trial in which genotype-guided dosing has been compared with standard dosing in warfarin-initiating patients, there was no difference in out of range INR in the first three months of therapy, although there was some improvement in stable warfarin dose predicting (13). The results of a recently developed pharmacokinetic-pharmacodynamic model for assessing the impact of *VKORC1* and *CYP2C9* genotype on warfarin response suggest that more research is needed to explore the effects of these genetic and other factors on the rate with which they affect anticoagulation response (14). The results of this model also suggest that the *CYP2C9* genotype is the single most important predictor of maintenance dose in an individual, which seems to accentuate its important role in individualizing warfarin therapy.

Until improved dose algorithms have been developed, it seems prudent to consider the *CYP2C9* variant status a risk factor for retarded stabilisation and increased risk of major bleeding and to monitor *CYP2C9* variant patients more intensely. More intense INR monitoring should be even considered when the *CYP2C9* variant status is identified in long-term users of coumarins.

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