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Review

Pharmacogenetics of oral anticoagulant therapy

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Abstract. Acenocoumarol and warfarin are among the most frequently used oral anticoagulants (OA) in the entire world. Their therapeutic index is narrow and there are many factors, including genetic ones, which interfere with their metabolism. The CYP2C9 and VKORC1 polymorphisms constitute the most important genetic factors that impede the correct anticoagulation. Algorithms which combine clinical and genetic parameters in order to predict a safe therapeutic dose of OA might be useful in reducing the risk of adverse effects.

Key Words: oral anticoagulant therapy, pharmacogenetics, CYP2C9, VKORC1, algorithms

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Introduction

In the last 70 years the antagonists of vitamin K (AVK) were the only therapeutic solution for oral anticoagulation in primary and secondary prophylaxis of arterial and venous thrombosis. The utility of AVK was demonstrated in many situations and presently they are taken by millions patients in the entire world. Many clinical and lab studies contributed to understanding of AVKs' pharmacokinetics and pharmacodynamics. Several studies were focused on the difficulty of AVK therapy management, more exactly on clinical and lab monitoring and on rapid methods of inhibiting their effects in case of overdose. Recently new oral anticoagulants (OAs) were authorized for commercialization: direct thrombin inhibitor (dabigatran exilate) and inhibitor of factor Xa inhibitor (rivaroxaban). The high cost of these new OAs and the lack of a specific antidote in case of hemorrhagic accidents, make AVKs treatment still the primary option. Acenocoumarol, warfarin and phenprocoumon are the most frequently used AVKs in the entire world. The fact that these drugs are among the top 5 substances that produce the most severe side effects is a paradox. Their therapeutic index is narrow. For a physician prescribing AVK, the main problem is to elaborate an adequate protocol for every patient. New ways of improving the management of AVK therapy are needed in order to ease the work of clinicians and to raise the safety of OAs.

Pharmacogenetics of AVK therapy

Pharmacogenetics studies the influence of genetics upon mechanisms which determines individual response to drug (therapeutic and side effects) (Klotz 2007). Along with the development of this branch of pharmacology, the studies were focused on the enzymes that catalyses AVK's metabolism in order to find out if there is a link between the genes that code these proteins and OAs therapeutic dose. In the '90s the important role of CYP2C9 for warfarin metabolism was demonstrated (Rettie *et al* 1992; Kaminsky *et al* 1997). About 8 years ago, VKOR (Vitamin K epoxide reductase) gene was identified and localized, fact that permitted studies which determined the link between AVK dose and the polymorphism VKORC1 (VKOR complex 1) (Li *et al* 2004; Wadelius *et al* 2005) .

CYP2C9

The cytochrome P450 (CYP) includes a superfamily of hemoproteins whose main function is final oxidation of organic substances (Nelson *et al* 1996). In humans, 57 gene and 59 pseudogenes that code CYP proteins were discovered (Nelson & Nebert 2011). CYP genes classification includes 18 families (represented by Arabic numbers) and 43 subfamilies (represented by letters) in conformity with the coded amino acid. Only 18 representatives (families 1 to 3) contribute substantially to drug metabolism (Wrighto & Stevens 1992). The rest of the enzymes are important for the metabolism of endogen substances. CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) is one of the four enzymes of a highly complex subfamily: CYP2C. CYP2C9 represents approximately 18% of the proteins that constitute CYP family in hepatic microsomes (Rettie & Jones 2006). CYP2C9 was purified for human liver and several variants of complementary DNA (cDNA) were isolated (Wang *et al* 1983; Yasumori *et al* 1987). CYP2C9 cDNA codes 490 amino acids with a molecular mass of 55.6 kDa. Six recognition regions were identified for CYP2C9 (Gotoh 1992). From studies of recognition sites, mutations, it was discovered that the ability of CYP2C9 to metabolize a certain substrate can be due to several critical residues or even a single amino acid. Several experiments were created in order to identify CYP isoforms which are implicated in every administered drug: investigation of correlation between drug rate of metabolism and immunoreactive CYP isoform from liver microsomes; comparison of drug metabolism and expression of cDNA; competitive inhibition of isoform's metabolism by the drug using liver

microsomes; characterisation of isoform's known specific effects or those of inhibiting antibodies upon drug metabolism (Miners & Birkett 1996). Although these studies were useful in linking the substrate from CYP2C9, the most effective method for defining the specific CYP2C9 substrate for certain drug was the inhibition of sulphaphenazole (Baldwin *et al* 1995).

Approximately 80-85% of S-enantiomer of warfarin is eliminated through biotransformation, catalysed by CYP, to 6-7 hydroxy-S-warfarin. The activity of the isoform responsible with the emergence of these metabolites regulates the concentration of S-warfarin and is the essential factor in the anticoagulant response. Presently it is known that CYP2C9 is the catalyst of S-warfarin hydroxylation at therapeutic concentration (Hall *et al* 1994; Kunze *et al* 1996). Tolbutamide and sulphaphenazole are selective inhibitors of these ways from liver microsomes (Rettie *et al* 1992).

In Europe and South America the most used AVKs are acenocoumarol and phenprocoumon. Acenocoumarol is the 4'-nitro analogue of warfarin. R-acenocoumarol has 8 hours half-time, approximately 4 times shorter than warfarin, and S-acenocoumarol has a half-time of 30 minutes. Acenocoumarol is eliminated also by 6-7 hydroxylation.

Metabolic clearance of S-acenocoumarol is high and that explain why the pharmacologic effect is provided almost exclusively by R-acenocoumarol (Thijssen *et al* 1985). Thijssen *et al* showed that S-acenocoumarol hydroxylation is mediated exclusively by CYP2C9 and R-acenocoumarol the expression of substrate of cDNA of CYP2C9. This is different from warfarin, whose R-enantiomer is barely metabolised. R-acenocoumarol is hydroxylated also by CYP1A2 and CYP2C19. When we take into consideration the kinetic of R-acenocoumarol hydroxylation by CYP2C9 and its high liver concentrations, it is expected of CYP2C9 to play the main role in vivo in 7-hydroxylation of R-acenocoumarol. Regarding 6-hydroxylation, in 40-50% of cases is catalysed by CYP2C9, in 20-30% by CYP1A2 and in 10-20% by CYP2C19 (Thijssen *et al* 2000). If we take into account this fact, as well as that warfarin is eliminated in 85% by CYP2C9, we may presume that the interaction of warfarin and acenocoumarol with substrates or inhibitors of CYP2C9 it will be different and genetic variants of CYP2C9 will affect differently drugs metabolism.

Phenprocoumon is a long-acting OA whose both isomers have a half-time of 5.5 days. Both of them are metabolised by CYP2C9. S-phenprocoumon is 2.5 time more potent than R-phenprocoumon (Haustein 1999).

The factors that influence the activity of CYP2C9 are grouped in inductors and inhibitors. The promoter region of CYP2C9 gene contains a sequence of 15 base pairs sensitive to induction by barbiturics (Goldstein & De Morais 1994). Administration of phenobarbital in patients that followed a long term treatment with warfarin determined a decrease of warfarin plasma concentration, which suggests the induction of S-warfarin metabolism (van Walraven *et al* 2006).

When and inhibitor of CYP2C9 is added to a therapeutic plan containing drugs with narrow therapeutic index (warfarin, tolbutamide, phenytoin) serious adverse effects can appear because of CYP2C9 decreased activity.

In 1979 studies reported the possible influence of genetics upon tolbutamide metabolism. Following this discovery possible locations of allelic variations were investigated, fact that lead to the confirmation of the existence of CYP2C9*2 and CYP2C9*3 variants with different frequency in Northern Europe (Stubbins *et al* 1996). Population studies showed that approximately 40% of Caucasians present at least one CYP2C9 allelic variant. Presently about 35 CYP2C9 alleles are known (CYP2C9 allele nomenclature). Polymorphisms from coding region of CYP2C9 gene determine variants at amino acids residues 144 and 359. Three major alleles, important for AVK metabolism, which came from C to T transposition (arginine to cysteine) and A to T (isoleucine to leucine) at 416 and 1061 codons were identified: Arg144/Ile359 (CYP2C9*1), Cys144/Ile359 (CYP2C9*2) and Arg144/Leu359 (CYP2C9*3) (Sullivan-Klose *et al* 1996). Table 1 shows prevalence of CYP2C9 polymorphism in different populations.

Table 1. Allelic frequency of CYP2C9 polymorphisms

Allele	Afro-Americans	Africans	Asians	Caucasians
CYP2C9*2	2.9	0-4.3	0-0.1	8-19
CYP2C9*3	2	0-2.3	1.1-3.6	3.3-16.2
CYP2C9*5	0-1.7	0.8-1.8	0	0
CYP2C9*6	0.6	2.7	0	0
CYP2C9*8	1.9	8.6	0	0
CYP2C9*9	13	15.7	0	0.3
CYP2C9*11	1.4-1.8	2.7	0	0.4-1.0

A recent study, conducted by Buzoianu *et al* (2012a), found an allele frequency of 11.3% for CYP2C9*2 and 9.3% for CYP2C9*3 in a Romanian population.

Subjects that carry those polymorphisms have a reduced capacity of metabolising S-warfarin, which leads to inadequate clearance of S-warfarin and to a prolonged half-time. CYP2C9*1 ("wild" type) metabolizes warfarin normally. Compared with normal homozygotes for CYP2C9*1, heterozygotes (CYP2C9*1*2, CYP2C9*1*3, CYP2C9*2*3) or abnormal homozygotes (CYP2C9*2*2, CYP2C9*3*3) necessitate smaller doses of OA (Lindh *et al* 2009). The presence of CYP2C9*2 lowers by 30% warfarin metabolism and the presence CYP2C9*3 lowers it by 90%. In patients treated with acenocoumarol, the presence of CYP2C9*3 reduced significantly S-acenocoumarol metabolism. In consequence, the isomer, normally clinically inactive, had a prolonged half-time and was the main factor responsible for the anticoagulant effect (Thijssen *et al* 2001). Several studies determined the fact that heterozygotes for CYP2C9*3 need smaller dose of acenocoumarol, as compared with those homozygotes "wild", and heterozygotes for CYP2C9*2 receive normal dose of acenocoumarol (Tàssies *et al* 2002; Buzoianu *et al* 2012b). The influence of CYP2C9 polymorphism on the frequency of hemorrhages during the initial phases of acenocoumarol treatment did not reveal a greater number of adverse events in patients heterozygotes or homozygotes for CYP2C9*2 or CYP2C9*3 (Militaru *et al* 2012a). Also CYP2C9 did not influenced the time required to reach the therapeutic INR (international normalized ratio) (Militaru *et al* 2012b).

There are several CYP genes whose mutations might influence AVK metabolism, beside CYP2C9. A polymorphism of CYP1A2 was identified as being partially responsible for metabolization of R-warfarin, but only in smokers (Sachse *et al* 1999). CYP3A1 contributes significantly to this process (Liang *et al* 2012). These polymorphisms are rarely met in general population, fact which explains the reduced impact on the AVK therapy.

VKORC1

Vitamins K represent a group of liposoluble vitamins, with similar structure, which have a role in posttranslational regulation of some key-proteins responsible of blood coagulation, bone and other tissues metabolism. The chemical structure is defined as 2-methyl-1,4-naphthoquinone (3-) derivatives. There are two main vitamins K: K1 and K2. Vitamin K1 is a stereoisomer of phylloquinone, a chemical compound found in green plants, where it has an important role in photosynthesis. Vitamin K1 is found in small quantities in roots or fruits and in much greater quantity in leaves (Bugel 2008; Booth & Al Rajabi 2008).

In humans, vitamin K suffers a dehydrogenation process, resulting vitamin K-hydroquinone. In the presence of calcium ions, vitamin K is implicated in the carboxylation of glutamic acid situated at the amino-terminal end of certain coagulation factors (procoagulant factors – II, VII, IX and X; anticoagulants factors – C, S and Z proteins), which leads to the formation of some gamma carboxyglutamate residues that will link with phospholipids (Mann 1999). Under the action of a epoxidase, hydroquinone is transformed in vitamin K – epoxide, which becomes vitamin K under the influence of an enzyme named Vitamin K epoxide reductase (VKOR). AVK inhibit the process of gamma-carboxylation of coagulation factors, as well as that of VKOR. The target region of AVK is the C1 subunit of VKOR (Goodstadt *et al* 2004).

VKOR was described for the first time in 1970, but the gene which codes it was cloned only in 2004. This gene is located on the short arm of chromosome 16. Several polymorphisms and haplotypes of VKORC1 (isoforms of VKOR which together form complex 1) determine the formation of enzymes with different sensibility to warfarin inhibition. In Caucasians and Asians, VKORC1 polymorphisms are responsible of 11-32% of dose variability of AVKs (Takahashi *et al* 2006). In Afro-Americans, VKORC1 polymorphisms explain 10% of dose variability (Momary *et al* 2007). Five of these polymorphisms define 2 haplotypes of Caucasian race: rs719616114 (381T>C or −4931T>C); rs9923231 (3673G>A or −1639G>A); rs9934438 (6484C>T or 1173C>T); rs8050894 (6853G>C or 1542G>C) and rs2359612 C>T (7566C>T or 2255C>T). These haplotypes are divides into haplotype A and haplotype B. Patients with haplotype A need low doses of warfarin, and those with haplotype B need high doses of warfarin (Rieder *et al* 2005).

The c.-1639G > A polymorphism of the VKORC1 gene was identified as the primary factor responsible of warfarin or acenocoumarol therapeutic efficiency (Montes *et al* 2006). The GG genotype ("wild") has no influence on warfarin dose. The GA genotype necessitates the reduction of warfarin dose by 20-28%, as compared with GG genotype. The AA genotype has the biggest impact, reducing the warfarin therapeutic dose by 40-50% (Sanderson *et al* 2005; Buzoianu *et al* 2012b).

Table 2. Frequency of VKORC1 allele in different races

VKORC1 genotype	Caucasians %	Asians %	Africans %
1173 TT	17	82	1
1173 CT	47	17	3
1173 CC	34	1.4	87
-1639/3673 AA	16	80	3
-1639/3673 GA	49	18	39
-1639/3673 GG	37	1.3	58
3730 GG	47	85	-
3730 AG	42	15	-
3730 AA	12	-	-

Clinical utility of AVK pharmacogenetics

One of the chief characteristics of therapy management of AVK is the difficulty to establish and maintain an efficient therapeutic dose, especially in the first day-weeks from its onset. This is because of genetic influence as well as external factors which affect vitamin K metabolism. An efficient anticoagulation is currently evaluated by INR values. The negative effects of intra and interindividual variability of AVK doses is situated at the extremities of INR spectrum. An overdose with AVK produces a high INR which represents an enhanced risk of hemorrhages. An INR below the therapeutic limit represents a high risk of a new venous thrombosis or of a stroke (in patients with atrial fibrillation). That is why several studies elaborated clinical and pharmacogenetic algorithms in order to improve the AVK treatment. Most of these studies focused on the first days of AVK therapy because of the high risk of adverse effects in this initial phase (Donohue & Tirschwell 2011).

In 2007 Food and Drug Administration adhered to the idea that genotyping could facilitate the identification of an optimal stable dose of warfarin, reducing in this way the frequency of hemorrhages (FDA 2007). Sconce *et al* (2005) proposed an algorithm that combined CYP2C9 and VKORC1 genotypes and height of patient in order to generate an initial estimative warfarin dose. Other studies showed that 60-65 of variation of warfarin dose can be explained by combination of genotypes with age and weight or body surface (Herman *et al* 2006; Vecsler *et al* 2006; Buzoianu *et al* 2012b). In Europeans and Americans CYP2C9 and VKORC1 polymorphisms are responsible of 30% of variability of warfarin dose, but only of 10% in Afro-Americans (Limdi *et al* 2008). There are studies which compared the time necessary for reaching a therapeutic INR in patients which used an AVK dose established by an algorithm that uses genotyping with patients that did not used a genetic-based algorithm. Anderson *et al* (2007) and Caraco *et al* (2008) did not found difference between those two methods, but Klein *et al* showed the superiority of the genetic-based algorithm.

Conclusions

The CYP2C9 and VKORC1 polymorphisms exert an important influence upon the metabolism and efficacy of AVK therapy. Genetic-based algorithms have the potential to improve the management of AVK therapy.

References

Ageno, W., Gallus, A. S., Wittkowsky, A., Crowther, M., Hylek, E. M., Palareti, G., 2012. Oral Anticoagulant Therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 141:2 suppl e44S-e88S.

Anderson, J. L., Horne, B. D., Stevens, S. M., Couma-Gen Investigators, et al, 2007. Randomized trial of genotype-guided versus standard warfarin dosing in patients initiating oral anticoagulation. Circulation 116(22):2563-2570.

Baldwin, S. J., Bloomer, J. C., Smith, G. J., Ayrton, A. D., Clarke, S. E., Chenery, R. J., 1995. Ketoconazole and sulphaphenazole as the respective selective inhibitors of P4503A and 2C9. Xenobiotica 25:261–270.

Bugel, S., 2008. Vitamin K and bone health in adult humans. Vitam Horm 78:393-416.

Booth, S. L., Al Rajabi, A., 2008. Determinants of vitamin K status in humans. Vitam Horm 78:1-22.

Buzoianu, A. D, Trifa, A. P., Mureşanu, D. F., Crişan, S., 2012a. Analysis of CYP2C9*2, CYP2C9*3 and VKORC1 -1639 G>A polymorphisms in a population from South-Eastern Europe. J Cell Mol Med 16(12):2919-24.

Buzoianu, A. D., Militaru, F. C., Vesa, S. C., Trifa, A. P., Crişan, S., 2012b. The impact of the CYP2C9 and VKORC1 polymorphisms on acenocoumarol dose requirements in a Romanian population. Blood Cells Mol Dis doi: 10.1016/j.bcmd.2012.10.010.

Caraco, Y., Blotnick, S., Muszkat, M., 2008. CYP2C9 genotype-guided warfarin prescribing enhances the efficacy and safety of anticoagulation: a prospective randomized controlled study. Clin Pharmacol Ther 83(3):460-470.

CYP2C9 allele nomenclature. Available at http://www.cypalleles.ki.se/cyp2c9.htm. Accessed at 15 December 2012.

Dieterle, W., Faigle, J. W., Montigel, C., Sulc, M., Theobald, W., 1977. Biotransformation and pharmacokinetics of acenocoumarol (Sintrom) in man. Eur J Clin Pharmacol 11:367–375.

Donohue, M. M., Tirschwell, D. L., 2011. Implications of pharmacogenetic testing for patients taking warfarin or clopidogrel. taking warfarin or clopidogrel. Curr Neurol Neurosci Rep 11(1):52-60.

FDA. FDA Approves Updated Warfarin (Coumadin) Prescribing Information. 2007 Available at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108967.htm. Accessed at 20 December 2012.

Goldstein, J. A., De Morais, S. M. F., 1994. Biochemistry and molecular biology of the human CYP2C subfamily. Pharmacogenetics 4:285–299.

Goodstadt, L., Ponting, C. P., 2004. Vitamin K epoxide reductase: homology, active site and catalytic mechanism. Trends Biochem Sci 29(6):289-92.

Gotoh, O. 1992. Substrate recognition sites in cytochrome P-450 family 2 (CYP2) proteins inferred from comparative analyses of amino acid and coding nucleotide sequences. J Biol Chem 267:83–90.

Hall, S. D., Hamman, M. A., Rettie, A. E., et al, 1994. Relationships between the levels of cytochrome P4502C9 and its prototypic catalytic activities in human liver microsomes. Drug Metab Dispos 22:975–978.

Haustein, K. O., 1999. Pharmacokinetic and pharmacodynamic properties of oral anticoagulants, especially phenprocoumon. Semin Thromb Hemost 25(1):5-11.

Herman, D., Peternel, P., Stegnar, M., Breskvar, K., Dolzan, V., 2006. The influence of sequence variations in factor VII, gamma-glutamyl carboxylase and vitamin K epoxide reductase complex genes on warfarin dose requirement. Thromb Haemost 95(5):782-787.

Kaminsky, L. S., Zhang, Z. Y., 1997. Human P450 metabolism of warfarin. Pharmacol Ther 73(1):67-74.

Klein, T. E., Altman, R. B., Eriksson, N., International Warfarin Pharmacogenetics Consortium, et al, 2009. Estimation of the warfarin dose with clinical and pharmacogenetic data. N Engl J Med 360(8):753-764.

Klotz, U., 2007. The role of pharmacogenetics in the metabolism of antiepileptic drugs: pharmacokinetic and therapeutic implications. Clin Pharmacokinet 46(4):271–9.

Kunze, K. L., Wienkers, L. C., Thummel, K. F., Trager, W. F., 1996. Warfarin-fluconazole I. Inhibition of human cytochrome P450 dependent metabolism of warfarin by fluconazole: in vitro studies. Drug Metab Dispos 24:414–421.

Li, T., Chang, C. Y., Jin, D. Y., Lin, P. J., Khvorova, A., Stafford, D. W., 2004. Identification of the gene for vitamin K epoxide reductase. Nature 427(6974):541-4.

Liang, R., Wang, C., Zhao, H., Huang, J., Hu, D., Sun, Y., 2012. Influence of CYP4F2 genotype on warfarin dose requirement-a systematic review and meta-analysis. Thromb Res 130(1):38-44.

Limdi, N. A., Arnett, D. K., Goldstein, J. A., et al, 2008. Influence of CYP2C9 and VKORC1on warfarin dose, anticoagulation attainment and maintenance among European-Americans and African-Americans. Pharmacogenomics 9(5):511-526.

Lindh, J. D., Holm, L., Andersson, M. L., Rane, A., 2009. Influence of CYP2C9 genotype on warfarin dose requirements - a systematic review and meta-analysis. Eur J Clin Pharmacol 65(4):365-375.

Mann, K. G., 1999. Biochemistry and physiology of blood coagulation. Thromb Haemost 82 (2):165–74.

Militaru, F. C., Crişan, S., Vesa, Ş. C., Trifa, A., Militaru, V., Buzoianu, A. D., 2012a. Determinants of hemorrhagic risk during acenocoumarol treatment. HVM Bioflux 4(1):23-28.

Militaru, F. C., Crişan, S., Vesa, Ş. C., Trifa, A., Militaru, V., Buzoianu, A. D., 2012b. Influence of CYP2C9 and VKORC1 polymorphisms on the time required to reach the therapeutic INR. HVM Bioflux 4(3):110-113.

Momary, K. M., Shapiro, N. L., Viana, M. A., Nutescu, E. A., Helgason, C. M., Cavallari, L. H., 2007. Factors influencing warfarin dose requirements in African-Americans. Pharmacogenomics 8(11):1535-1544.

Montes, R., Ruiz de Gaona, E., Martínez-González, M. A., Alberca, I., Hermida, J., 2006. The c.-1639G > A polymorphism of the VKORC1 gene is a major determinant of the response to acenocoumarol in anticoagulated patients. Br J Haematol 133(2):183-7.

Miners, J. O., Birkett, D. J., 1996. The use of tolbutamide as a substrate probe for human hepatic cytochrome P4502C9. Methods Enzymol 272:139–145.

Nelson, D. R., Koymans, L., Kamataki, T., et al, 1996. P450 superfamily: Update on new sequences, gene mapping, accession numbers and nomenclature. Pharmacogenetics 6:1–42.

Nelson, D. R, Nebert, D. W., 2011. Cytochrome P450 (CYP) Gene Superfamily. In: Encyclopedia of Life Sciences (ELS). John Wiley & Sons, Ltd: Chichester.

Rettie, A. E., Korzekwa, K. R., Kunze, K. L., Lawrence, R. F., Eddy, A. C., Aoyama, T., et al, 1992. Hydroxylation of warfarin by human cDNA-expressed cytochrome P-450: a role for P-4502C9 in the etiology of (S)-warfarin-drug interactions. Chem Res Toxicol 5(1):54-9.

Rettie, A. E., Jones, J. P., 2006. Clinical and toxicological relevance of CYP2C9: Drug-Drug Interactions and Pharmacogenetics. Annu Rev Pharmacol Toxicol 45: 477–94.

Rieder, M. J., Reiner, A. P., Gage, B. F., et al, 2005. Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose. N Engl J Med 352:2285–2293.

Sachse, C., Brochmoller, J., Bauer, S., et al, 1999. Functional significance of C > A polymorphism in intron 1 of the cytochrome P450 CYP1A2 gene tested with caffeine. Br J Clin Pharmacol 47:445-449.

Sanderson, S., Emery, J., Higgins, J., 2005. CYP2C9 gene variants, drug dose, and bleeding risk in warfarin-treated patients: a HuGEnet systematic review and meta-analysis. Genet Med 7(2):97-104.

Sconce, E. A., Khan, T. I., Wynne, H. A., et al, 2005. The impact of CYP2C9 and VKORC1 genetic polymorphism and patient characteristics upon warfarin dose requirements: proposal for a new dosing regimen. Blood 106 (7):2329-2333.

Stubbins, M. J., Harries, L. W., Smith, G., Tarbit, M. H., Wolf, C. R., 1996. Genetic analysis of the human cytochrome P450 CYP2C9 locus. Pharmacogenetics 6:429–39.

Sullivan-Klose, T. H., Ghanayem, B. I., Bell, D. A., et al, 1996. The role of the CYP2C9-Leu (359) allelic variant in the tolbutamide polymorphism. Pharmacogenetics 6:341–349.

Takahashi, H., Wilkinson, G. R., Nutescu, E. A., et al, 2006. Different contributions of polymorphisms in VKORC1 and CYP2C9 to intra- and inter-population differences in maintenance dose of warfarin in Japanese, Caucasians and African-Americans. Pharmacogenet Genomics 16(2):101-110.

Tàssies, D., Freire, C., Pijoan, J., Maragall, S., Monteagudo, J., Ordinas, A., Reverter, J. C., 2002. Pharmacogenetics of acenocoumarol: cytochrome P450 CYP2C9 polymorphisms influence dose requirements and stability of anticoagulation. Haematologica 87(11):1185-91.

Thijssen, H. H. W., Janssen, G. M. J., Baars, L. G. M., 1985. Lack of effect of cemitidine on pharmacodynamics and kinetics of single oral doses of R- and S-acenocoumarol. Eur J Clin Pharmacol 30:619–623.

Thijssen, H. H., Flinois, J. P., Beaune, P. H., 2000. Cytochrome P4502C9 is the principal catalyst of racemic acenocoumarol hydroxylation reactions in human liver microsomes. Drug Metabol Dispos 28:1284-1290.

Thijssen, H. H. W., Drittij, M. J., Vervoort, L. M. T., de Vries-Hanje, J. C., 2001. Altered pharmacokinetics of R- and S-acenocoumarol in a subject heterozygous for CYP2C9*3Altered pharmacokinetics of R- and S-acenocoumarol in a subject heterozygous for CYP2C9*3. Clin Pharmacol Ther 70:292-298.

Vecsler, M., Loebstein, R., Almog, S., et al, 2006. Combined genetic profiles of components and regulators of the vitamin K dependent gamma-carboxylation system affect individual sensitivity to warfarin. Thromb Haemost 95(2):205-211.

Wadelius, M., Chen, L. Y., Downes K., Ghori, J., Hunt, S., Eriksson, N., et al, 2006. Common VKORC1 and GGCX polymorphisms associated with warfarin dose. Pharmacogenomics J 5(4):262-70.

van Walraven, C., Jennings, A., Oake, N., Fergusson, D., Forster, A. J., 2006. Effect of study setting on anticoagulation control: a systematic review and metaregression. Chest 129(5):1155-66.

Wrighton, S. A., Stevens, J. C., 1992. The human hepatic cytochromes P450 involved in drug metabolism. Crit Rev Toxicol 22:1–21.

Wang, P., Beaune, P., Kaminsky, L. S., et al, 1983. Purification and characterization of six cytochrome P450 isozymes from human liver microsomes. Biochemistry 22:5375–383.

Yasumori, T. S., Kawano, K., Nagata, M., Shimada, Y., Yamazoe, Y., Kato, R., 1987. Nucleotide sequence of a human liver cytochrome P450 related to the male rat specific form. J Biochem (Tokyo) 102:1075–1082.

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