# The *CYP2C9* polymorphism: from enzyme kinetics to clinical dose recommendations

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CYP2C9 is the major human enzyme of the cytochrome P450 2C subfamily and metabolizes approximately 10% of all therapeutically relevant drugs. Two inherited SNPs termed *CYP2C9*2* (Arg144Cys) and *3 (Ile359Leu) are known to affect catalytic function. Numerous rare or functionally silent polymorphisms have been identified. About 35% of the Caucasian population carries at least one *2 or *3 allele. CYP2C9 metabolizes several oral hypoglycemics, oral anticoagulants, non-steroidal anti-inflammatory drugs and other drugs, including phenytoin, losartan, fluvastatin, and torsemide. *In vitro* studies with several drugs indicate that the Cys144 (.2) and Leu359 (.3) variants confer only about 70 and 10% of the intrinsic clearance of the wild-type protein (.1), respectively. The clinical pharmacokinetic implications of these polymorphisms vary depending on the enzymes contribution to total oral clearance. Several studies demonstrated that the *CYP2C9* polymorphisms are medically important for non-steroidal anti-inflammatory drugs, for oral hypoglycemics, vitamin K antagonistic oral anticoagulants, and phenytoin. In particular, *CYP2C9* polymorphisms should be routinely considered in therapy with oral anticoagulants where severe adverse events at initiation of therapy might be reduced by genotyping. *CYP2C9* polymorphisms were also clinically associated with side effects of phenytoin, with gastric bleeding during therapy with non-steroidals and with hypoglycemia under oral hypoglycemic drugs. Data appear mature enough for the routine consideration of *CYP2C9* genotypes in therapy with acenocoumarol, phenytoin, warfarin, and some other drugs. Nevertheless, it is advisable before the routine clinical use of these genotype data to rigorously test the benefits of genotype-based therapeutic recommendations by randomized controlled clinical trials.

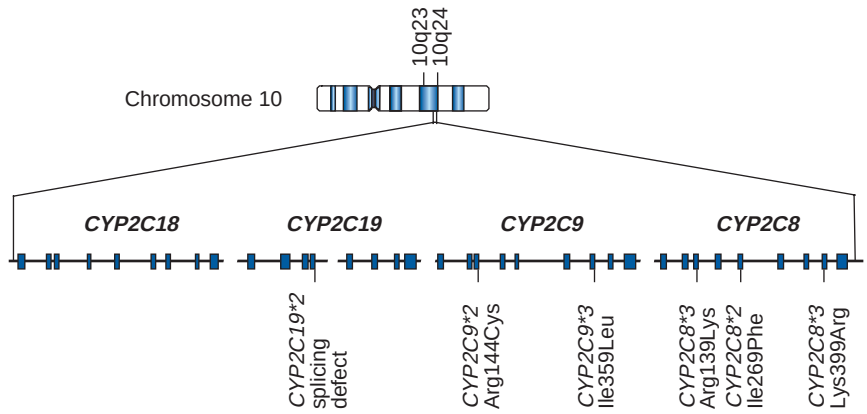
Keywords: CYP2C9, cytochrome P450, individualization, pharmacogenetics, pharmacogenetics-based dose adjustment

Members of the cytochrome P450 (CYP) 2C enzyme subfamily are the most important phase I oxidative drug-metabolizing enzymes. The genes coding for these enzymes are mapped on chromosome 10, between q23 and q24, in the order of *CYP2C18*, *2C19*, *2C9* and *2C8* [1] (Figure 1). Next to the enzyme CYP3A4, CYP2C9 is the most predominantly expressed CYP enzyme in the human liver and, by far, the most highly expressed of the 2C subfamily. It metabolizes approximately 10% of therapeutically relevant drugs. Two inherited amino acid substitutions, Arg144Cys (*2) and Ile359Leu (*3), are known to affect catalytic functions of CYP2C9 [2-4]. Allele frequencies in Caucasians are about 82% for the wild-type allele *CYP2C9*1*, 11% for *CYP2C9*2*, and 7% for *CYP2C9*3* [5], resulting in genotype frequencies of 65.3, 20, 0.9, 12, 1.4 and 0.4% for the *CYP2C9* diplotypes *1/*1, *1/*2, *2/*2, *1/*3, *2/*3, and *3/*3, respectively [6]. There may be minor differences in frequencies of these genotypes between different ethnic subgroups of the Caucasian populations and the variant *CYP2C9*2* is almost absent in African and Asian populations. Besides *CYP2C9*2* and *3, many other genetic variants have been described within *CYP2C9* [6,8-12], but the frequency of most of these alleles is low or the polymorphisms do not lead to an amino acid exchange [201]. In Table 1, allele frequencies of the most prevalent alleles are given for the major ethnic groups. A null-allele (*CYP2C9*6*) with complete enzyme deficiency has also been described, and a homozygous genotype with this allele has been found in one individual [9].

Several variants have been described in the 5′-flanking region of the *CYP2C9* gene, and the *CYP2C9*3* has been strongly associated with a 60% reduction of luciferase activity [7]. But the functional effects of the *CYP2C9*3* allele can also be fully explained by the functional changes conferred by the Ile359Leu amino acid substitution, as reported in Figure 2.

CYP2C9 metabolizes all clinically used vitamin K antagonists, almost all sulfonylurea oral

**Figure 1. Schematic representation of the *CYP2C* gene locus on chromosome 10.**




Note that intronic and intergene distances are much larger than represented in this figure and the entire *CYP2C* gene locus spans an area of about 500,000 nucleotides. The genomic localization of selected medically important polymorphisms is shown. There is extensive linkage between several polymorphisms within the entire *CYP2C* gene locus and this linkage has to be considered in the interpretation of clinical pharmacogenetic studies. For instance, two completely linked polymorphisms of the allele *CYP2C8*3* are also tightly linked with the *CYP2C9*2* allele [145], and several polymorphisms in *CYP2C18* are linked with those in *CYP2C19*. Another major polymorphism of *CYP2C19,* termed **3*, is localized in close proximity to *CYP2C19*2*.

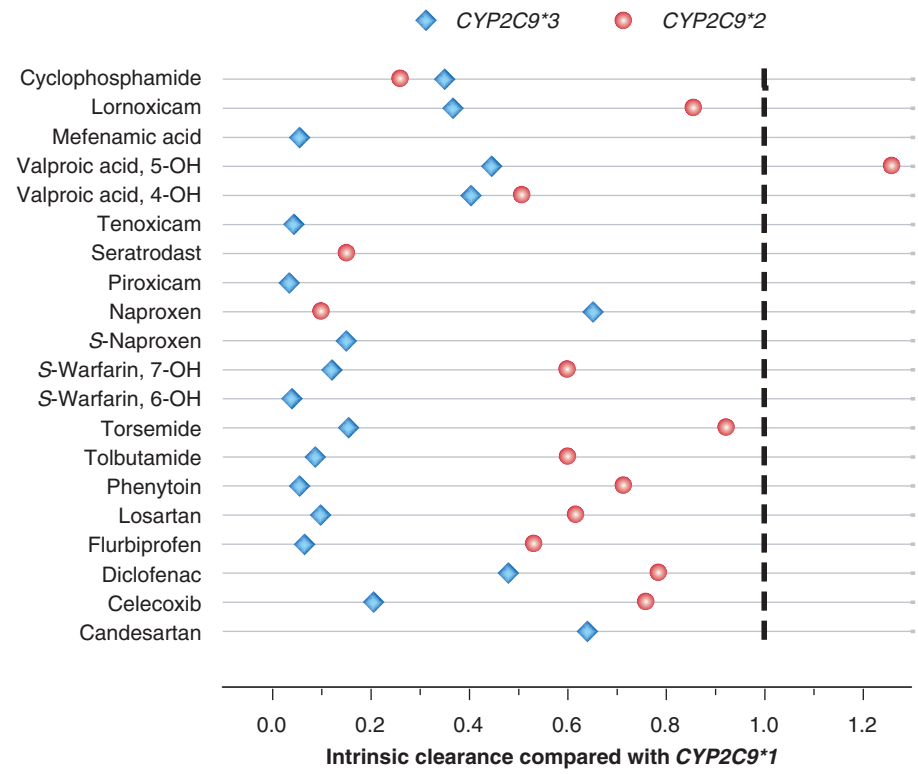
**Table 1. Frequency of the *CYP2C9* alleles in different populations.**

| Allele | Nucleotide changes | Exon location | Protein variation | Activity compared with *CYP2C9*1/*1* | Allele frequency | | |
|---|---|---|---|---|---|---|---|
| | | | | | Africans | Asians | Caucasians |
| *CYP2C9*2* | *430C→T* | Exon 3 | Arg144Cys | Decrease | 4% | 0% | 11% |
| *CYP2C9*3* | *1075A→C* | Exon 7 | Ile359Leu | Decrease | 2% | 3% | 7% |
| *CYP2C9*4* | *1076T→C* | Exon 7 | Ile359Thr | - | 0% | - | 0% |
| *CYP2C9*5* | *1080C→G* | Exon 7 | Asp360Glu | Decrease | 1.8% | - | 0% |
| *CYP2C9*6* | *818delA* | Exon 5 | Null allele | No activity | 0.6% | - | 0% |
| *CYP2C9*7* | *55C→A* | Exon 1 | Leu19Ile | - | - | - | - |
| *CYP2C9*8* | *449G→A* | Exon 3 | Arg150His | Increase | 6.7% | - | - |
| *CYP2C9*9* | *752A→G* | Exon 5 | His251Arg | Decrease | - | - | - |
| *CYP2C9*10* | *815A→G* | Exon 5 | Glu272Gly | - | - | - | - |
| *CYP2C9*11* | *1003C→D* | Exon 7 | Arg335Trp | Decrease | 2.7% | - | 0.4% |
| *CYP2C9*12* | *1465C→D* | Exon 9 | Pro489Ser | Decrease | - | 2% | - |

*Summarized frequency data from [6,10,82,114-120]. A hyphen indicates lack of sufficient data. Note that such allele frequencies may even differ within the major ethnic groups.*
*CYP: Cytochrome P450.*

hypoglycemic drugs, the majority of the non-steroidal anti-inflammatory drugs (NSAIDs), several angiotensin receptor antagonists, and a number of drugs belonging to various classes, including phenytoin, fluvastatin, torsemide, and $\Delta^9$-tetrahydrocannabinol. In addition, CYP2C9 is capable of metabolizing a number of steps in arachidonic acid and linoleic acid metabolism, as well as several metabolic reactions in sexual steroids [13], but the quantitative contribution of CYP2C9 compared with other enzymes, such as CYP2J2 and CYP2C8, to these reactions in humans is not yet clear. Arachidonic acid metabolites are involved in the regulation of vascular tone, and one case-control study in Swedish subjects with acute myocardial infarction revealed a slightly higher risk for those individuals carrying *CYP2C9* or *CYP2C8* variants (odds ratio was 1.3) [14]. Table 2 gives an overview of the endogenous and exogenous substances that are

**Figure 2. Effect of the amino acid substitutions Arg144Cys in *CYP2C9* allele **2* (red circles) and Ile359Leu in *CYP2C9* allele **3* (blue rhombs) according to *in vitro* data.**




The intrinsic clearances are depicted relative to the intrinsic clearance of the wild-type enzyme (*CYP2C9*1*, shown as black bars). Intrinsic clearance was calculated as $V_{max}/K_m$ and the study citations are given in Table 3; if there was more than one study, the mean of the studies are shown. See Table 3 for further details of the reactions catalyzed by CYP2C9 in these drugs.

metabolized in at least one metabolic pathway by CYP2C9 according to *in vitro* or *in vivo* data. The number of clinical trials in which the *CYP2C9* polymorphisms were confirmed to play a role in drug metabolism are small, as reviewed in detail below.

Clinical studies have been performed in patients and in healthy subjects characterizing the contribution of the *CYP2C9*2* and **3* polymorphisms to pharmacokinetic variability in humans, and a great impact has been found for a number of drugs. However, this knowledge is not yet considered in clinical practice. Pharmacogenetics, in general, is a new field in medicine, and clinicians are mostly unaware that failure to respond to a drug, an exaggerated drug effect or an idiosyncratic adverse drug reaction might be caused by the pharmacogenetic genotypes of an individual. There are a number of reasons why pharmacogenetics is only slowly entering into clinical practice but one important reason may be that many studies were not optimally designed to allow application of pharmacogenetics in the clinic. A pharmacogenetic diagnostic test result has to be followed by distinct therapeutic advice. For example, a genotype leading to decreased metabolic activity should be followed by a defined adjustment of the individual drug dosage or by choosing a different therapeutic strategy. Without specific guidelines on how to use genotypes in personalized drug therapy, the pharmacogenetic knowledge about polymorphic drug metabolism will never be used for the benefits of patients [15]. Moreover, without specific rules on how to apply available genotype information, these new types of diagnostics may not even reach the required prospective randomized clinical trials.

This article intends to summarize the preclinical and clinical data on the impact of the *CYP2C9* polymorphisms on the drugs that are CYP2C9 substrates. However, to enable specific

**Table 2. Xenobiotic and endobiotic substrates for CYP2C9 with at least one metabolic pathway mediated by CYP2C9 according to *in vitro* or *in vivo* data.**

| Drugs | | | |
|---|---|---|---|
| ***NSAIDs*** | ***Anti-infectives*** | ***Oral hypoglycemics*** | ***Hypnotics, antiepileptics*** |
| Aceclofenac | Dapsone | Rosiglitazone | Phenobarbital |
| Acetyl salicylic acid | Sulfadiazine | Troglitazone | Hexobarbital |
| Azapropazone | Sulfamethoxazole | Tolbutamide | Phenytoin |
| Celecoxib | Trimethoprim | Glibenclamide | Valproate |
| Diclofenac | Terbinafine | Glimepiride | Temazepam |
| Flurbiprofen | Azidothymidine | Glipizide | Zopiclon |
| *S*-Ibuprofen | Nelfinavir | Nateglinide | Zolpidem |
| Indomethazine | Nevirapine | | |
| Lornoxicam | | | |
| Mefenaminic acid | | | |
| Meloxicam | ***Angiotensin-2 antagonists*** | ***Oral anticoagulants*** | ***Psychotropics*** |
| *S*-Naproxen | Losartan | *S*-Warfarin | *R*-Fluoxetine |
| Phenylbutazone | Candesartan | *S*-Phenprocoumon | Moclobemide |
| Piroxicam | Irbesartan | *R,S*-Acenocoumarol | Sertraline |
| Suprofen | | Dicoumarol | Venlafaxine |
| Tenoxicam | | | Perazine |
| Valdecoxib | | | Perphenazine |
| ***Analgesics*** | ***Leukotriene antagonists, lipoxygenase inhibitors*** | ***Diuretics*** | ***Others*** |
| Paracetamol | Zafirlukast | Torasemide | Fluvastatin |
| Antipyrine | Zileuton | Tienilinic acid | Tetrahydro-cannabinol |
| Aminopyrine | | | Sildenafil |
| Amidopyrine | | | Seratrodast |
| Phenacetin | | | Carvedilol |
| **Toxins** | | | |
| ***Polycyclic aromatic hydrocarbons*** | ***Insecticides, herbicides*** | ***Others*** | |
| Benzo[a]pyren | Chlorpyrifos | Ochratoxin A | |
| Dibenzo[a]pyren | Methoxychlor | Nicotine | |
| Naphthalene | | | |
| **Endobiotic substrates** | | | |
| ***Steroidals*** | ***Synthetic hormones*** | ***Fatty acids*** | |
| Estradiol | Desogestrel | Arachidonic acid | |
| Estrone | Tamoxifen | Linolenic acid | |
| Progesterone | | | |
| Testosterone | | | |

*Data from [13,121].*
*NSAID: Non-steroidal anti-inflammatory drug.*

therapeutic recommendations to be given, clinical studies must be sufficiently powerful and, in this respect, many of the data compiled in this present review are derived from insufficient sample sizes and more research is urgently needed. If *CYP2C9* genotyping should become a routine part of future clinical practice, the concept of drug dosing based on genotype diagnostics should be studied in prospective randomized clinical trials, at least for some examples.

The data presented in this paper were retrieved from public databases, such as Medline and Embase, and from the drug information brochures, such as those provided by the manufacturer. The following keyword searches were used (alone and in combination with the substrate names) in order to obtain all clinical and *in vitro* enzyme kinetic data on *CYP2C9* polymorphisms: CYP2C9; variant; polymorphism; polymorphic; microsome(s); metabolism; *in vitro*; $K_m$ (Michaelis constant); and $V_{max}$ (velocity of enzyme catalyzed reaction at infinite concentration of substrate). For the *in vitro* data analysis, all studies on polymorphic CYP2C9 expression systems in yeast, baculovirus systems or liver microsomes were included, but not

studies with CYP2C9 inhibitors. $V_{max}$ and $K_m$ values were extracted from the studies and listed for each of the *CYP2C9*1*, **2* and **3* alleles, and intrinsic clearance was calculated as $V_{max}/K_m$.

For clinical data retraction, all data from studies in patients or healthy volunteers evaluating pharmacokinetic parameters, such as oral clearance, steady-state concentrations or area under the concentration–time course (AUC), were included. It has to be noted that the *CYP2C9* polymorphism may have an impact on drug bioavailability and also on drug systemic clearance. The effects on bioavailability may be due to the CYP2C9 effects in first-pass metabolism, and large differences in the maximum blood concentration ($C_{max}$) of the drug between the *CYP2C9* genotype groups might indicate CYP2C9-mediated first-pass metabolism. However, a final analysis on this question would require studies with oral and intravenous administration, which have not been performed in this context. Therefore, the meta-analysis has been restricted to the total oral clearance differences, which were calculated as dose/$AUC_{0\text{-infinity}}$ and which included the bioavailability differences. Studies that only contained information on metabolic ratios in urine were not included since these parameters are not related to dose in a linear manner and, therefore, cannot be used for dose adjustments based on pharmacokinetic differences.

### *In vitro* data on *CYP2C9*2* and **3*

*In vitro* data on the impact of the CYP2C9 Arg144Cys variant (the single amino acid substitution encoded by *CYP2C9*2*) and on the Ile359Leu variant (the single amino acid substitution encoded by *CYP2C9*3*) was found for a total of 18 drugs. For the other drugs mentioned in this review, no data on the enzyme kinetic differences between the three CYP2C9 variant proteins, .1, .2 and .3, were found. The available data are summarized in Table 3, and a graphical representation is given in Figure 2. As can be seen, intrinsic clearance by the *CYP2C9*2* encoded protein was reduced to around 70% compared to the wild type, with only a few exceptions (Figure 2).

For the CYP2C9.3 protein, which has the amino acid substitution Ile359Leu, the median intrinsic clearance was often only about 10% compared to the wild-type enzyme. From this picture one may draw a general conclusion that there are little drug-specific differences concerning the impact of the .2 and .3 protein variants. As can be summarized from Table 3, the Ile359Leu amino acid substitution coded by the *CYP2C9*3* allele leads to a significantly lower $V_{max}$ and higher $K_m$ value compared with the wild type, while the Arg144Cys substitution coded by the **2* variant results in a moderate reduction in $V_{max}$ and, in most cases, there is no change in $K_m$. Recent crystallographic data confirmed that the Ile359Leu variation is located in proximity to the active center in the so-called substrate recognition site 5 and, therefore, might determine access to the catalytic center or substrate binding [16]. However, the codon 144 amino acid substitution is located outside the active center but may play a role in the interaction of CYP2C9 with CYP reductase [17].

The results from the *in vitro* data related to isolated expressed enzymes exclusively reflect the effects of the amino acid variants of CYP2C9. Predicting human *in vivo* pharmacokinetics from *in vitro* enzyme kinetic data is still imprecise [18]. Often, clearance is mediated by multiple phase I and II enzymes and, depending on the drug substrate, their relative contribution to pharmacokinetics is difficult to estimate from the *in vitro* data. In addition, drug transporters and renal clearance contribute to interindividual pharmacokinetic variability. Thus, in the development of new drugs that are CYP2C9 substrates or in the clinical pharmacogenetic analysis of 'old' drugs, which are also CYP2C9 substrates, clinical pharmacokinetic trials in carriers of the various *CYP2C9* genotypes are indispensable.

### Summary of human clinical pharmacokinetic data

In Table 4, the clinical data on pharmacokinetic differences due to the *CYP2C9* genotypes are listed. Corresponding to the *in vitro* findings, *CYP2C9*3* has much stronger effects on pharmacokinetics than *CYP2C9*2*. Individuals carrying the homozygous genotype *CYP2C9*3/*3* had a 5- to 10-fold reduced total oral clearance (calculated as dose/AUC) compared with wild type and this was dependent on the substrate. Thus, for many drugs metabolized by CYP2C9 (e.g., glibenclamide, nateglinide, ibuprofen, celecoxib, phenytoin, tolbutamide, glipizide, and *S*-warfarin) a large decrease in metabolic activity due to the *CYP2C9*3* allele was observed. A lower or non-existant effect of *CYP2C9*2* on the pharmacokinetic parameters was observed for a number of drugs, but a decreased extrarenal clearance and a higher risk of bleeding complications was shown in carriers of the *CYP2C9*2* allele when administered *S*-warfarin [19,20].

**Table 3. Summary of the *CYP2C9* genotype-specific enzyme kinetic data.**

| Drug | Metabolite | *CYP2C9*1* | | *CYP2C9*2* | | *CYP2C9*3* | | Ref. |
|---|---|---|---|---|---|---|---|---|
| | | $K_m$‡ | $V_{max}$§ | $K_m$‡ | $V_{max}$§ | $K_m$‡ | $V_{max}$§ | |
| Candesartan | M-II | 345.0 | 1.1 | | | 439.0 | 0.5 | [123] |
| Celecoxib | Methylhydroxycelecoxib | 3.3 | 8.9 | 2.4 | 4.1 | 3.6 | 0.9 | [85] |
| | | 5.1 | 2.1 | 5.9 | 2.1 | 11.0 | 1.2 | [124] |
| Diclofenac | 4'-Hydroxydiclofenac | 3.9 | 35.6 | | | 12.6 | 33.3 | [82] |
| | | 1.8 | 12.5 | 2.5 | 11.2 | 11.1 | 8.1 | [80] |
| | | 2.0 | 12.4 | | | 16.5 | 17.9 | [2] |
| | | 4.8 | 29.0 | | | 17.0 | 13 | [8] |
| | | 7.4 | 25.8 | 5.6 | 11.5 | 24.3 | 26.95 | [125] |
| | | 32.8 | 1.5¶ | 20.5 | 0.7¶ | 6.0 | 0.156¶ | [75] |
| | | 25.9 | 57.9 | | | 46.9 | 138.1 | [127] |
| Flurbiprofen | 4'-Hydroxyflurbiprofen | 5.3 | 5.9 | 8.3 | 3.1 | 31.0 | 2.6 | [80] |
| | | 33.5 | 3.3 | 29.2 | 2.1 | 170.0 | 0.76 | [114] |
| *S*-Flurbiprofen | *S*-4'-Hydroxy-flurbiprofen | 19.4 | 9.6 | | | 71.7 | 2.5 | [128] |
| Fluvastatin | 6'-Hydroxyfluvastatin | 0.9 | 0.08 | 1.2 | 0.06 | | | [93] |
| | 5'-Hydroxyfluvastatin | 1.0 | 0.04 | 1.0 | 0.03 | | | [93] |
| | N-Deisopropyl fluvastatin | 1.8 | 0.04 | 1.3 | 0.03 | | | [93] |
| Losartan | E3174 | 5.3 | 0.9 | 3.7 | 0.4 | 6.7 | 0.16 | [125] |
| | | 4.4 | 33.5 | 5.4 | 24.5 | 5.1 | 2.1 | [125] |
| Phenytoin | 4'-Hydroxyphenytoin | 15.0 | 0.2 | | | 30.0 | 0.015 | [82] |
| | | 10.0 | 0.1 | 10.0 | 0.1 | 40.0 | 0.019 | [129] |
| Tolbutamide | Hydroxytolbutamide | 145.0 | 0.6 | 122.0 | 0.4 | 745.0 | 0.373 | [3] |
| | | 106.0 | 1.9 | 72.0 | 1.2 | | | [130] |
| | | 151.0 | 9.2 | | | 1729.0 | 10 | [82] |
| | | 43.0 | 10.6 | 92.9 | 1.5 | 477.0 | 5.2 | [131] |
| Torsemide | Methylhydroxy-torsemide | 40.0 | 5.2 | 24.0 | 2.8 | 85.0 | 1.7 | [108] |
| *S*-Warfarin | *S*-7'-Hydroxywarfarin | 11.6 | 0.1 | 12.5 | 0.2 | 92.3 | 0.2 | [3] |
| | | 18.0 | 0.2 | 22.0 | 0.1 | 53.0 | 0.067 | [80] |
| | | 6.0 | 0.2 | 6.0 | 0.1 | 30.0 | 0.041 | [129] |
| | | 5.6 | 0.1 | | | 28.0 | 0.02 | [8] |
| | | 2.6 | 0.3 | | | 10.4 | 0.07 | [35] |
| | | 4.1 | 0.4 | 1.7 | 0.03 | | | [130] |
| | | 5.8 | 0.2 | | | 21.6 | 0.111 | [82] |
| | | 6.0 | 0.2 | | | 30.0 | 0.041 | [132] |
| | | 28.0 | 0.2 | | | 55.1 | 0.13 | [127] |
| *S*-Warfarin | *S*-6'-Hydroxywarfarin | 6.8 | 0.1 | | | 31.0 | 0.009 | [132] |
| *R*-Warfarin | *R*-4'-Hydroxywarfarin | 20200 | 212 | 3400 | 82.6 | 10600 | 384.6 | [3] |
| *S*-Naproxen | *S*-Demethylnaproxen | 89.1 | 1.4 | | | | | [128] |
| Naproxen | Demethylnaproxen | 248.0 | 2.6 | 122.0 | 0.7 | | | [114] |
| Piroxicam | 5'-Hydroxypiroxicam | 40.0 | 0.4 | | | 61.0 | 0.019 | [82] |
| | | 30.5 | 0.2 | | | 29.5 | 0.007 | [128] |
| Seratrodast | 4'-Hydroxyseratrodast | 27.5 | 0.1 | 76.0 | 0.1 | | | [133] |
| | 5'-Hydroxyseratrodast | 16.5 | 0.4 | 47.4 | 0.2 | | | [133] |
| Tenoxicam | 5'-Hydroxytenoxicam | 28.0 | 0.3 | | | 90.0 | 0.034 | [82] |

‡$K_m$ *was measured in µmol/l.* §$V_{max}$ *was measured in pmol/min/pmol CYP unless otherwise stated.*

¶*In these experiments the unit of* $V_{max}$ *measurement was pmol/min/mg protein.*

*CYP: Cytochrome P450;* $K_m$*: Michaelis constant;* $V_{max}$*: Velocity of enzyme-catalyzed reaction at infinite concentration of substrate.*

**Table 3. Summary of the *CYP2C9* genotype-specific enzyme kinetic data (continued).**

| Drug | Metabolite | *CYP2C9*1* | | *CYP2C9*2* | | *CYP2C9*3* | | Ref. |
|---|---|---|---|---|---|---|---|---|
| | | $K_m$‡ | $V_{max}$§ | $K_m$‡ | $V_{max}$§ | $K_m$‡ | $V_{max}$§ | |
| Valproic acid | 4'-Hydroxyvalproic acid | 11,000 | 7.3 | 16,000 | 5.3 | 36,000 | 9.51 | [134] |
| | 5'-Hydroxyvalproic acid | 4000 | 2.9 | 5000 | 1.7 | 20,000 | 2.36 | [134] |
| Mefenamic acid | 3'-Hydroxymefenamic acid | 8.4 | 14.9 | | | 40.8 | 4.2 | [82] |
| Lornoxicam | 5'-Hydroxylornoxicam | 0.8 | 0.4 | 0.9 | 0.5 | 2.0 | 0.097 | [135] |
| | 5'-Hydroxylornoxicam | 0.9 | 0.2 | 0.8 | 0.1 | 1.2 | 0.144 | [135] |
| Cyclophosphamide | 4-Hydroxycyclo-phosphamide | 2900 | 27.8 | 5850 | 14.7 | 3750 | 12.45 | [136] |

‡$K_m$ *was measured in µmol/l.* §$V_{max}$ *was measured in pmol/min/pmol CYP unless otherwise stated.*

¶*In these experiments the unit of* $V_{max}$ *measurement was pmol/min/mg protein.*

*CYP: Cytochrome P450;* $K_m$*: Michaelis constant;* $V_{max}$*: Velocity of enzyme-catalyzed reaction at infinite concentration of substrate.*

## *CYP2C9* polymorphisms and oral hypoglycemic drugs

In Figure 3, the *CYP2C9* genotype-specific changes in the oral clearance of oral hypoglycemic drugs are depicted, summarizing all the available data from Table 4. If data were obtained from more than one study, the information was means weighted according to the sample size and coefficients of variation.

### *Tolbutamide*

More than 80% of tolbutamide is eliminated by hepatic biotransformation to hydroxytolbutamide. This tolyl hydroxylation is the rate-limiting metabolic step and is almost exclusively catalyzed by CYP2C9 in humans. In three individuals with the genotype *CYP2C9*3/*3*, oral clearance was only 16% (0.15 l/h) compared with individuals carrying the wild-type alleles (0.97 l/h) [21]. Individuals heterozygous for the *CYP2C9* allele **3* had an oral clearance value that fell between those for the homozygous and the wild-type patients (0.56 l/h). Differences due to the **2* allele were much less pronounced; homozygotic carriers (**2/*2*; n = 3) had an oral clearance of approximately 75% of the values for wild-type carriers, and no distinguishable differences were found in heterozygous carriers (**1/*2*) [21]. In two other studies [22,23], subjects expressing the *CYP2C9*1/*2* and *CYP2C9*1/*3* genotypes demonstrated significantly reduced oral clearances of tolbutamide and a lower amount of excreted 4-hydroxytolbutamide in the urine, showing that both amino acid substitutions in CYP2C9 cause decreased enzyme activity.

The aim of another recent study was to evaluate tolbutamide in the low dose of 125 mg as a probe drug for CYP2C9 phenotyping. The researchers found that the oral clearances remained in the same ranges as obtained from the studies using 500 mg tolbutamide, which indicates linear pharmacokinetics within this dose range [24]. The oral clearances of the individuals grouped by genotypes *CYP2C9*1/*3* and **2/*2* were significantly lower ($p < 0.001$) than the oral clearances in the high-activity genotype groups *CYP2C9*1/*1* and **1/*2*.

The clinical relevance of CYP2C9-mediated differences in the oral clearance of tolbutamide is presumably low since tolbutamide is infrequently used in current treatment regimens. With respect to drug research and drug development, however, this study confirms that tolbutamide, even when administered in a 125-mg test dose, is an appropriate and relatively safe probe drug for CYP2C9, which can be used in drug–drug interaction studies and in further functional genomic studies on the *CYP2C9* gene locus. Alternatively, *S*-warfarin is recommended by drug investigators and by regulatory authorities as a phenotyping substrate [25] and other substrates have also been proposed, including losartan [26].

### *Glyburide*

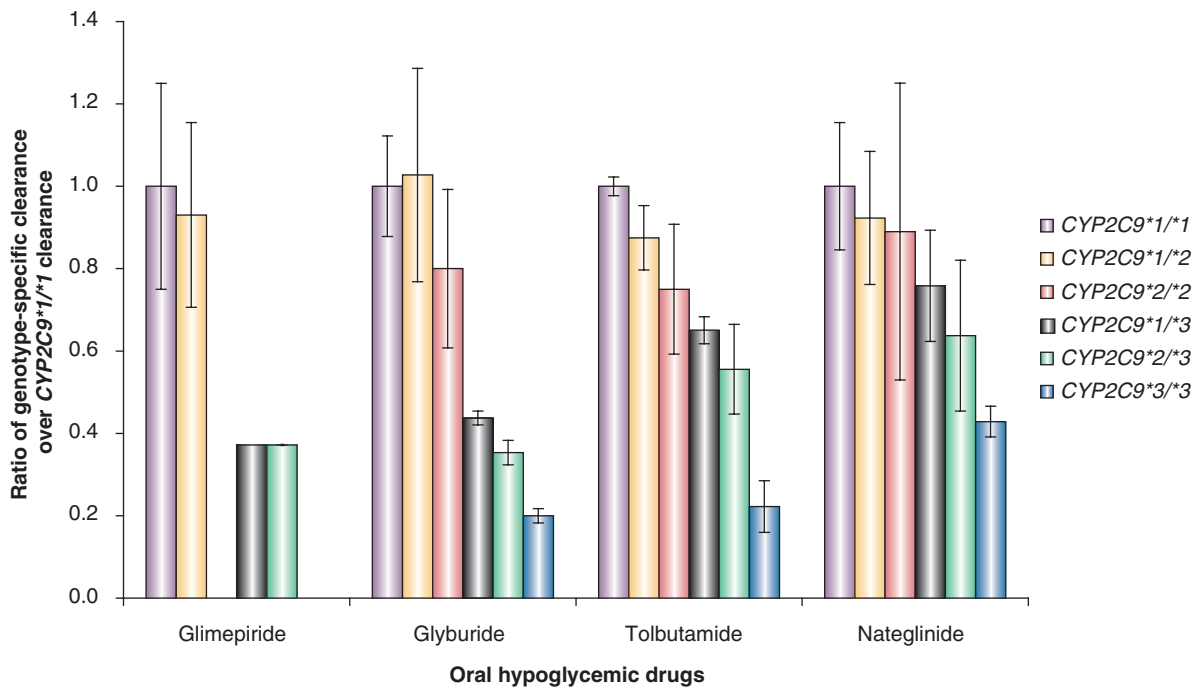
CYP2C9 plays a major role in the biotransformation of glyburide in humans, whereas the hydroxylation phenotype, debrisoquine (CYP2D6) or mephenytoin (CYP2C19), did not correlate with glyburide metabolism [27]. In homozygous carriers of the *CYP2C9* allele **3*, oral clearance was only 50% of the respective values measured in carriers of the homozygous wild-type genotype [28]. In heterozygous carriers of the genotypes *CYP2C9*1/*3* or *CYP2C9*2/*3*, significantly higher AUCs were reported in two

**Table 4. Quantitative difference in total oral clearance due to the *CYP2C9* polymorphisms, which serves as a basis for pharmacokinetically derived dose adjustments.**

| | Pharmacokinetics, mean total oral clearance (l/h) | | | | | | Sample size‡ | Ref. |
|---|---|---|---|---|---|---|---|---|
| | *1/*1 | *1/*2 | *2/*2 | *1/*3 | *2/*3 | *3/*3 | | |
| ***Oral anticoagulants*** | | | | | | | | |
| *S*-Acenocoumarol | 19.8 | | | 10.9 | | | 3/0/0/0/3/0 | [56] |
| | 0.5§ | 0.2§ | | 0.4§ | 2§ | | 170/45/0/32/9/0 | [137] |
| *S*-Phenprocoumon | 0.057 | 0.047 | 0.044 | 0.053 | 0.038 | 0.045 | 7/4/3/4/5/3 | [64] |
| | 0.22 | 0.13 | 0.12 | 0.11 | 0.06 | 0.024 | 118/32/2/27/6/3 | [38] |
| *S*-Warfarin | 39.6¶ | 22.8¶ | 12.8¶ | 20.7¶ | 9.3¶ | 3.66¶ | 54/15/2/16/4/2 | [20] |
| ***Hypoglycemics*** | | | | | | | | |
| Glimepiride | 4.3 | 4 | | 1.6 | 1.6 | | 12/5/0/2/1/0 | [29] |
| Glyburide | 3.5 | 4.3 | 2.9 | 2.5 | 1.9 | 0.7 | 4/4/3/3/4/3 | [28] |
| | 7.8 | 7.8 | | 2.8 | 2.8 | | 5/3/0/1/1/0 | [29] |
| Tolbutamide | 0.9 | 1 | 0.7 | 0.5 | 0.5 | 0.2 | 6/4/3/3/4/3 | [21] |
| | 0.78 | | | 0.6 | | | 12/0/0/6/0/0 | [22] |
| | 0.9 | 0.6 | | 0.5 | | | 5/5/0/0/5/0 | [23] |
| | 0.9 | 0.8 | 0.6 | 0.6 | | | 15/7/1/3/0/0 | [24] |
| Nateglinide | 9.1 | 8.4 | 8.1 | 6.9 | 5.8 | 3.9 | 7/4/3/5/4/3 | [138] |
| ***Angiotensin antagonists*** | | | | | | | | |
| Candesartan | 109 | | | 52.6 | | | 6/0/0/1/0/0 | [92] |
| Losartan | 125 | 73 | | 110 | | | 5/5/0/0/5/0 | [139] |
| | 64 | 72 | 57 | 87 | 54 | 39 | 6/3/3/4/5/1 | [87] |
| ***Non-steroidal anti-inflammatory drugs*** | | | | | | | | |
| Celecoxib | 30 | 42 | 48 | 21 | 33 | 9 | 4/4/3/3/4/3 | [140] |
| | 38 | 43 | 32 | 25 | | 43 | 10/6/2/0/4/1 | [72] |
| | 45 | 45 | | 18 | | 15 | 12/2/0/0/2/1 | [85] |
| Diclofenac | 53 | 58 | 31 | 70 | | 76 | 10/6/2/0/4/1 | [72] |
| | 20 | 29 | 30 | 22 | 41 | 23 | 3/4/3/3/4/4 | [74] |
| | 46 | 29 | 53 | 31 | 24 | 63 | 6/3/1/4/5/1 | [75] |
| | 22 | | | 30 | | | 6/0/0/0/6/0 | [141] |
| Flurbiprofen | 1.7 | 1.3 | | 1 | | | 5/5/0/5/0/0 | [81] |
| *S*-Ibuprofen | 3.3 | 3.2 | 3.1 | 2 | 2.4 | 1.5 | 4/4/3/3/4/3 | [78] |
| | 5.2 | 4.8 | 2.0 | 3.6 | 1.2 | 0.9 | 69/34/4/11/7/5 | [79] |
| Tenoxicam | 0.11 | 0.08 | | 0.06 | | | 11/4/0/5/0/0 | [83] |
| ***Others*** | | | | | | | | |
| (3*S*5*R*)-Fluvastatin | 88 | 95 | 70 | 56 | 38 | 18 | 5/4/3/4/5/3 | [94] |
| Phenytoin | 2.35 | | | | | 0.5 | | [142] |
| | 5.3# | | | 4.1 | | | | [102] |
| | 4.2# | 5.5 | 6.6 | 5.7 | | 5.9 | 68/13/3/16/0/1 | [103,143] |
| | 287‡‡ | 201 | 217 | 196 | 175 | | 37/9/3/9/2/0 | [104] |
| | 0.84 | 0.56 | 0.31 | 0.57 | 0.31 | | 18/7/1/4/1/0 | [144] |
| Torsemide | 3.5 | 3.7 | 2.3 | 2.2 | 1.9 | 1.2 | 12/9/1/9/3/2 | [145] |

‡*Sample size in the* CYP2C9 *diplotype groups* *1/*1, *1/*2, *2/*2, *1/*3, *2/*3, *and* *3/*3. §*Steady-state concentrations are given in ng/ml.*
¶*The unbound oral clearance of warfarin is given in this article which is ~100-fold smaller compared with the total oral clearance as given in the paper by Herman et al. [37].* #*Trough concentrations measured 12 h after a single dose of 300 mg are given in mg/l.*
‡‡*Mean daily doses are given in mg. This means that therapeutically adjusted doses were recorded and then genotyping was performed which revealed significant dependence of therapeutically adjusted dose from the CYP2C9 genotype.*
*CYP: Cytochrome P450.*

**Figure 3. Data on the differences in oral clearances of the specific oral hypoglycemic drugs due to *CYP2C9* genotypes.**




All data are summarized by calculating weighted means from the specific study's data based on the sample sizes in each of the genotype groups. Standard deviations of the studies were transformed to variation coefficients and are depicted in the figure. References for the studies in this figure are summarized in Table 4. In this histogram and in the histograms in Figures 4, 6, and 7, the effect of the genotypes are presented as reduction relative to the clearances measured in carriers of the *CYP2C9*1/*1* genotype group.

individuals compared to the remaining eight individuals with genotypes *CYP2C9*1/*1* or **1/*2* [29]. Allele **2* only marginally reduced CYP2C9 activity in glyburide metabolism; oral clearance in homozygous carriers of allele **2* was about 80% of the value reported in wild-type carriers.

The differences in glyburide pharmacokinetics that depend on the *CYP2C9* genotype were reflected in differences in insulin plasma concentrations and in insulin secretion; however, the magnitude of differences between the genotype groups was much lower than those reported for the pharmacokinetic parameters [28]. In part, this discrepancy may be due to active glyburide metabolites, but these metabolites have not yet been quantified in clinical pharmacogenetic trials [28,29].

There may be a significant risk for hypoglycemia in recipients of sulfonylurea antidiabetic drugs, which are mostly used in ambulatory medicine. Recent and, as yet, unpublished data from our group indicate that carriers of the **2/*3* and **3/*3* genotypes may have a fivefold increased risk for severe hypoglycemia (Holstein *et al.* [30]). Such observations require confirmation in larger samples of patients but this might indeed by an example where *CYP2C9* genotyping might help to reduce adverse events.

### *Glipizide*

Similar to glyburide, CYP2C9 has been shown to be involved in glipizide metabolism. Largely reduced (≤ 20% of the control value measured in wild-type carriers) glipizide oral clearance has been reported in one homozygous carrier of the *CYP2C9*3* allele [9]. The reduction of oral clearance in this carrier of the *CYP2C9*3/*3* genotype is even greater than reported for glyburide; however, one must keep in mind that this finding is from a single case report. Due to the structural similarity of both these second-generation sulfonylurea drugs (differing only in the aryl ring portion), a similar role of CYP2C9 in hydroxylation can be anticipated.

### *Glimepiride*

One clinical study on glimepiride pharmacokinetics and CYP2C9 reported AUC ratios of larger than 2 between individuals who were heterozygous for the *CYP2C9*3* allele and those who were homozygous for the wild-type allele. No statistically significant differences were reported between heterozygous individuals for the *CYP2C9*2* allele and wild-type carriers. Furthermore, no data from homozygous carriers of these *CYP2C9* alleles are available; however, assuming a linear gene–dose effect, differences similar to tolbutamide can be expected for the *CYP2C9*3/*3* carriers if the heterozygous group already differs twofold. Based on the present pharmacokinetic knowledge, if physicians are aware that a patient is a *CYP2C9*1/*3* or *3/*3* carrier, then they could recommend starting therapy with about half of the standard dose in *CYP2C9*1/*3* carriers, and with even lower doses in the homozygous *3/*3* individuals. However, in the lack of strong pharmacodynamic and clinical efficiency-based data, the accuracy of dose-adjustment recommendations for oral antidiabetics can be debated. Nonetheless, it seems to be clinically more safe if physicians are informed of the *CYP2C9* genotype status of a patient, especially in regard to the *CYP2C9*3* allele, so that patients at risk can be carefully monitored for hypoglycemia.

### *Nateglinide*

Nateglinide is an oral antidiabetic drug that has more recently been introduced on the market and that preferentially stimulates the early insulin secretion, thereby preventing the extensive postprandial glucose excursions that are seen in Type 2 diabetes. Nateglinide is a CYP2C9 substrate and the AUC, total clearance and $C_{max}$ of the compound showed a statistically significant difference between the *CYP2C9* genotype groups when stratified for carriers of zero, one or two *CYP2C9*3* alleles; the differences between carriers of *2 alleles and wild-type carriers were not significant. However, the magnitude of the *CYP2C9*3*-related difference was moderate [138] with a mean clearance in *1/*3 and *3/*3 carriers of 76 and 43% of the wild-type value (compare Figure 3 and Table 4). Earlier pharmacokinetic/pharmacodynamic analyses indicated that the *CYP2C9* genotype might only be relevant when nateglinide is used in doses above 120 mg [138].

## Oral anticoagulants

Numerous studies on the impact of *CYP2C9* polymorphisms for bleeding complication and dose finding in warfarin and acenocoumarol therapy have been performed, and some major trials are still ongoing. Pharmacokinetic differences between the *CYP2C9* genotypes are well documented for *S*-warfarin, *S*-acenocoumarol, and *S*-phenprocoumon. As summarized in Figure 4, these differences were much smaller for phenprocoumon when compared with those of warfarin and acenocoumarol.

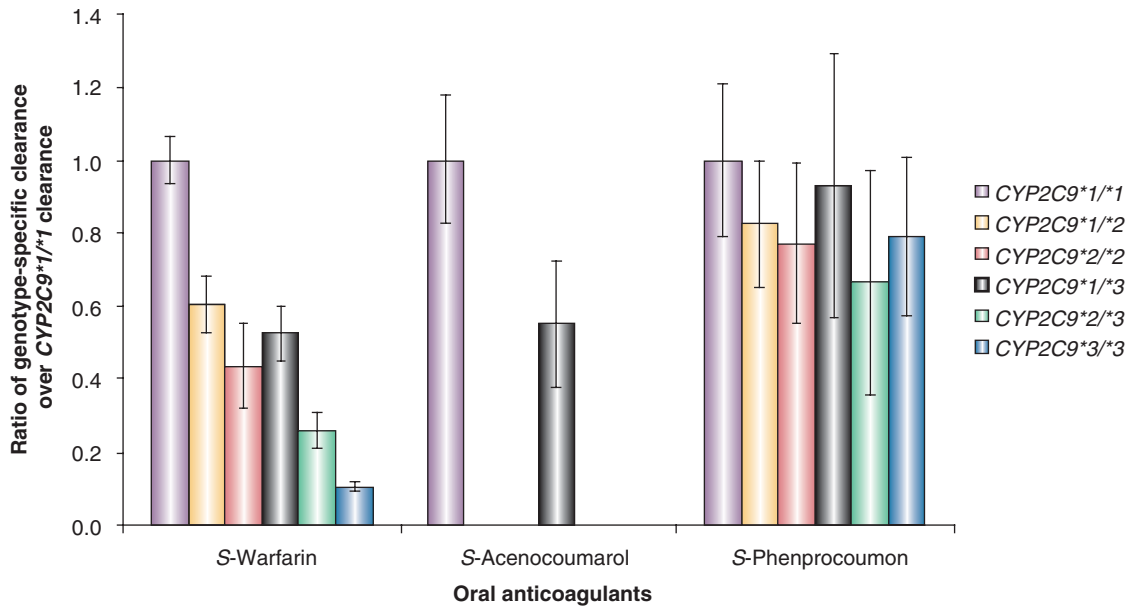
### *Warfarin*

The hepatic biotransformation of warfarin is highly regio- and stereoselective. The pharmacologically more potent *S*-enantiomer is preferentially metabolized by CYP2C9 to 6- and 7-hydroxywarfarin, whereas CYP1A2, CYP2C19 and CYP3A4 are the major enzymes involved in the hydroxylation of *R*-warfarin [31-33]. Both variants, *CYP2C9*2* and *CYP2C9*3*, have influence on the pharmacokinetics of *S*-warfarin; however, the effect of the *CYP2C9*2* variant was less pronounced [20,34-36]. The majority of the studies evaluating the effects of *CYP2C9* polymorphisms on metabolism, clinically adjusted dosing and bleeding complications have been reviewed by Takahashi [37].

Based on current pharmacokinetic data, it can be concluded that individuals with *CYP2C9*1/*2* and *2/*2* genotypes would require approximately 80 and 32% of the standard dose of warfarin administered to wild-type CYP2C9 carriers, respectively. Using the same principle, patients with the *1/*3*, *2/*3* and *3/*3* genotypes would only need 56, 23 and 9% of the standard dose, respectively [20,38], but adjustments based on clinical effects may be less pronounced, as discussed below.

The majority of the studies performed in this area have assessed the impact of the *CYP2C9* polymorphisms in warfarin treatment not from measurements of the kinetics, but from measurements of effects, such as the internationally normalized ratio (INR; which reflects the extent of anticoagulation), adverse event monitoring or analysis of clinically adjusted daily drug doses. Patients carrying one or two variant *CYP2C9* alleles had a higher incidence of supratherapeutic INR values (> 4), required a longer time to achieve stable dosing and reported a higher rate of serious or life-threatening bleeding events during initiation of warfarin therapy [39-42]. Differences in mean daily doses according to the *CYP2C9* genotype were observed in patients who were dosed empirically by measurement of the INR. These differences may be considered as

**Figure 4. Data on the differences in oral clearances of the specific oral anticoagulants due to *CYP2C9* genotypes.**




All data are summarized by calculating weighted means from the specific study's data based on the sample sizes in each of the genotype groups. Standard deviations of the studies were transformed to variation coefficients and are depicted in the figure. References for the studies summarized in this figure are provided in Table 4.

good estimates of how doses might be adjusted according to the *CYP2C9* genotype. However, these differences were less pronounced compared to the differences in pharmacokinetic parameters. According to the effect-monitoring data, daily doses should be reduced to 87 and 82% of the standard doses in carriers of the **1/*2* and **2/*2* genotypes, respectively. Doses in carriers of **1/*3*, **2/*3* and **3/*3* should be reduced to only 68, 57 and 33% of the standard doses, respectively. These data were retrieved from several clinical studies, and means were calculated according to the sample size [36,37,40,42-51]). Concerning the question as to why the differences derived from clinically adjusted doses were smaller than those derived from the pharmacokinetic-based adjustments, one might consider that the *R*-enantiomer also contributes to the effect.

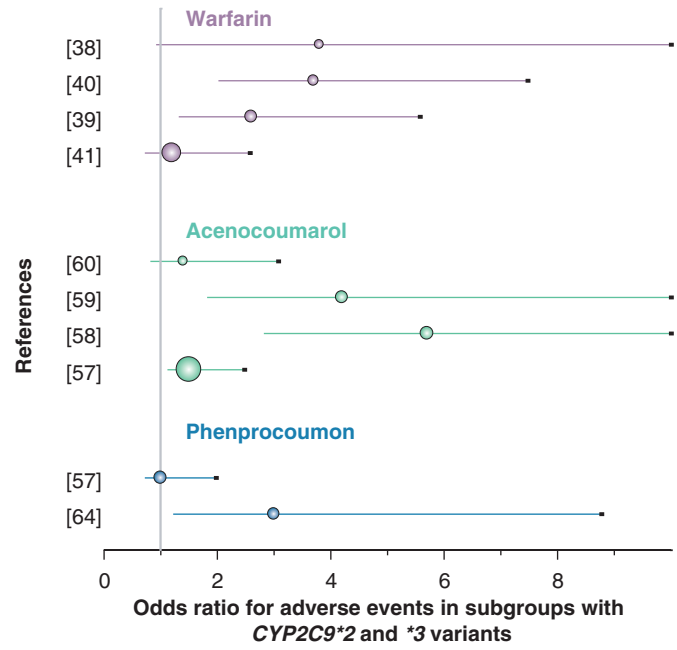
Whereas one could argue that the INR measurement-based dose findings might appear sufficient, reports showing a higher frequency of bleeding complications in **2* and **3* carriers during the initiation of treatment [42] suggest that genotype-based dose adjustments might be additionally useful. All these data are so convincing that drug therapy with warfarin is most likely to be the first example of *CYP2C9* genotyping in clinical practice.

Several more pharmacogenetic polymorphisms have also been shown to interfere with the efficacy and adverse effects of warfarin, such as variants within the vitamin K epoxide reductase (*VKORC1*) [51-53]. In recent years, there has been a trend toward the use of lower doses of warfarin, resulting in a more safe therapy. Safety may even be further increased by including *CYP2C9* and possibly *VKORC1* genotyping.

### *Acenocoumarol*

*CYP2C9* polymorphisms seem to play a less important role in acenocoumarol therapy, since both enantiomers of the compound contribute to the pharmacodynamic effect. However, the active *R*-acenocoumarol has a longer elimination time and higher tissue concentrations and is metabolized by several CYPs, including CYP1A2, CYP2C9, CYP2C19, and CYP3A4 [54]. For acenocoumarol, pharmacokinetic differences due to the *CYP2C9*3* allele have been described, as well as differences in empirically obtained daily doses: heterozygous carriers of *CYP2C9*3* had only 40% of the oral clearance

**Figure 5. Risk for a major adverse effects (namely, bleeding complications) of oral anticoagulants in carriers of *CYP2C9*2* and *3 alleles.**




The dots indicate the relative risk with the size of dots representing the sample size and, thus, the power of the respective studies and the bars indicate the 95% confidence intervals of the risk estimates. Note that a relative risk of unity (1) means that there is no risk associated with the *CYP2C9* genotypes and that there was a trend to lower risk estimates in the larger studies. Such trends might indicate some publication bias; in particular, this might indicate that there should also have been smaller studies with inverse risk estimates that have never been published.

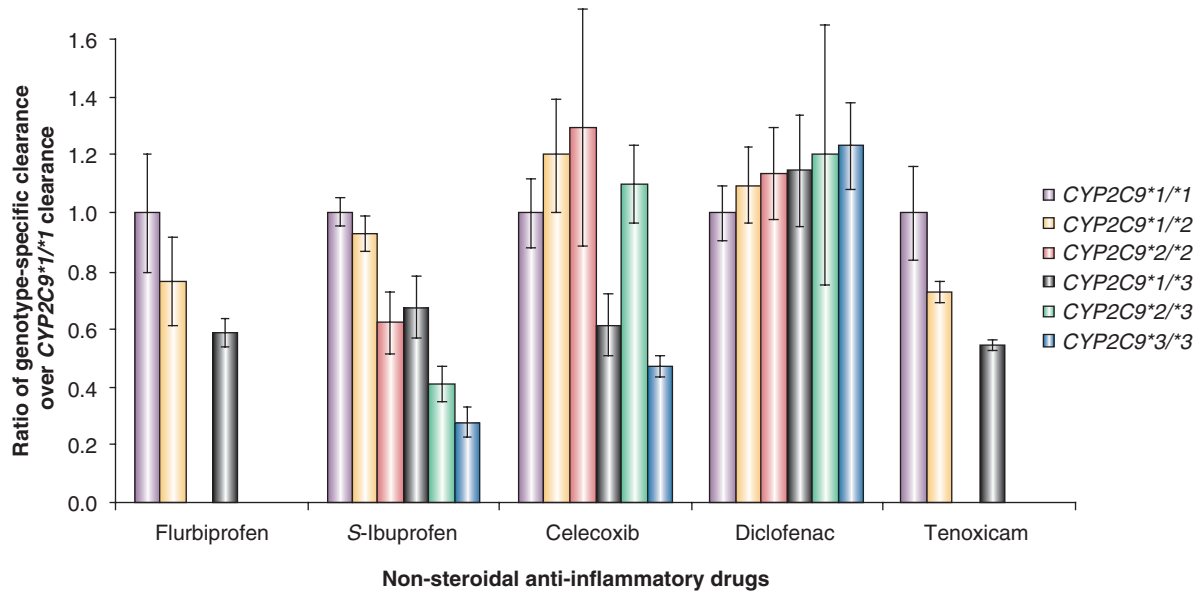
measured in *CYP2C9*1/*1* carriers, whereas clinical monitoring resulted in a mean daily dose that was 70% in **1/*3* carriers compared with 100% in the wild type [55-59]. A higher risk for bleeding complications was described in carriers of the *CYP2C9* variants [58] and a higher incidence of severe overanticoagulation with INRs > 6 was evident in *CYP2C9*3* carriers [59-61] (Table 4). Thus, similar to warfarin, other inherited factors, including the *VKORC1* polymorphisms mentioned above, should also be considered.

Consistent with the fact that the kinetics of acenocoumarol are not exclusively determined by CYP2C9, Morin *et al.* found, within an unselected sample, that only 14% of pharmacodynamic variability was related to CYP2C9 [137]. This should, however, not detract from the hypothesis that *CYP2C9* genotyping might result in a significant improvement in acenocoumarol therapy, particularly at the initiation of therapy.

### *Phenprocoumon*

Clinical drug–drug interaction data and *in vitro* enzyme kinetic data with human liver microsomes and recombinant enzymes have suggested a moderate impact of the *CYP2C9* polymorphisms for phenprocoumon [62,63]. Only relatively small pharmacokinetic differences that are dependent on the *CYP2C9* genotype were detected in humans after a single dose of 12 mg of phenprocoumon. For the active *S*-phenprocoumon, the mean oral clearance was 57, 48 and 37 ml/h in **1/*1*, **1/*3* and **3/*3* carriers, respectively; a difference which was only statistically significant when calculating the *S*- to *R*-enantiomer ratio [64]. Whether or not these minor differences have any clinical significance appears questionable. In one clinical trial, no effects of *CYP2C9* polymorphisms on the dose requirements were reported [58]. However, another study found an about threefold increase in the risk of bleeding in carriers of *CYP2C9*1/*3* [65] (Table 4 and Figure 5).

**Figure 6. Data on the differences in oral clearances of the specific non-steroidal anti-inflammatory drugs due to *CYP2C9* genotypes.**




All data are summarized by calculating weighted means from the specific study's data based on the sample sizes in each of the genotype groups. Standard deviations of the studies were transformed to variation coefficients and are depicted in the figure. References for the studies summarized in this figure are presented in Table 4.

## Non-steroidal anti-inflammatory drugs

At least 16 different registered NSAIDs are currently known to be at least partially metabolized via CYP2C9. These are aceclofenac, acetylsalicylic acid, azapropazone, celecoxib, diclofenac, flurbiprofen, ibuprofen, indomethacin, lornoxicam, mefenamic acid, meloxicam, naproxen, phenylbutazone, piroxicam, suprofen, and tenoxicam [13]. Thus far, the relative contribution of *CYP2C9* polymorphisms to variability in pharmacokinetics and effects of the compounds in humans has only been studied for a few NSAIDs (Figure 6). Observational studies in patients taking NSAIDs that are CYP2C9 substrates showed a threefold elevated relative risk for acute upper gastrointestinal bleeding in individuals carrying *CYP2C9* genetic variants compared with those carrying the wild-type gene [66].

### *Diclofenac*

*In vitro* studies with human hepatocytes, liver microsomes and transgenically expressed CYP enzymes indicated that CYP2C9 almost exclusively catalyzes the 4′-hydroxylation of diclofenac [67-70], as well as hydroxylation to the minor metabolite 3′-hydroxydiclofenac [70]. However, hydroxylation at the 5′-position appeared to be catalyzed predominantly by CYP3A4, as well as by CYP2C19, CYP2C8, and CYP2C18 [67,68,70,71].

In contrast and unexpectedly from the *in vitro* data, the pharmacokinetics of diclofenac was found to be independent of *CYP2C9* polymorphisms in several independent clinical trials [72-75]. Correspondingly, neither diclofenac-induced hepatitis nor gastric ulceration appeared to be related to the *CYP2C9* polymorphisms [19,76].

### *Ibuprofen and flurbiprofen*

Ibuprofen is a racemic mixture of the active *S*-enantiomer and the much less active *R*-ibuprofen. Recently, *S*-ibuprofen was introduced into the market as an isolated enantiomer. *In vitro* studies indicate stereoselective hydroxylation of ibuprofen with CYP2C8 and CYP2C9 being the main enzymes involved in the hydroxylation of *R*-ibuprofen and *S*-ibuprofen, respectively [77].

Pharmacokinetic differences in *S*-ibuprofen revealed that carriers of one or two alleles *CYP2C9*3* had only 65 and 31% of the oral clearance compared with extensive metabolizers (mean values of the studies [78] and [79]). Oral clearances were reduced to 66% of the control group in *CYP2C9*2/*2* carriers (mean values

from [78] and [79]). The differences were reflected in the duration of cyclooxygenase 1 (COX-1) and COX-2 inhibition [78]. Gastritis, ulcer and minor or even major upper intestinal bleeding, analgesic nephropathy or fluid retention are typical dose-related adverse events of NSAIDs like ibuprofen. Recently, the frequency of *CYP2C9* polymorphisms was reported to be higher in patients suffering from acute gastric bleeding complications after NSAID use [66,76] (Table 4).

Flurbiprofen is another CYP2C9 substrate [79], and individuals with the *CYP2C9*1/*3* genotype had only 60% of the oral clearance of the wild-type carriers [81].

### *Tenoxicam*

Tenoxicam is also known to be a CYP2C9 substrate and hydroxylation is markedly decreased in carriers of the *CYP2C9*3* allele [82]. A clinical study revealed a mean oral clearance in *CYP2C9*1/*3* genotype carriers that was 55% of the clearance seen in wild-type carriers [83]. Tenoxicam is a long-acting non-steroidal agent and this long duration of action may cause high risks for gastric bleeding or other adverse effects. It is not unlikely that this risk may be even greater in carriers of *CYP2C9*3*, but this assumption has not yet been confirmed in clinical trials.

### *Celecoxib*

CYP2C9 was shown to be the major enzyme mediating celecoxib methyl hydroxylation [84,85]. Celecoxib is one of the first COX-2-selective NSAIDs for which the manufacturer's drug information recommends caution when administering celecoxib to poor metabolizers of CYP2C9 substrates because they may have abnormally high plasma levels.

Several clinical studies revealed a large influence of the *CYP2C9*3* alleles on celecoxib metabolism with a mean oral clearance in *CYP2C9*1/*3* and *3/*3* carriers that was reduced to 70 and 30% of the clearance in wild-type carriers, respectively. The clinical impact, however, is not evident since celecoxib has a quite broad therapeutic range; in particular, the risk for gastrointestinal bleeding is smaller than for other non-steroidal compounds. Thus, it is somewhat surprising that there is a warning accompanying the use of warfarin but not for the other drugs that show greater CYP2C9-influenced pharmacokinetic differences. However, due to the involvement of COX-2 in physiological processes other than pathological inflammation, *CYP2C9* polymorphisms should be considered in pharmacoepidemiological evaluations concerning this COX-2-selective drug. Recent data on rofecoxib (which is not a CYP2C9 substrate) showed that this drug class may indeed have medically significant adverse cardiovascular effects [86].

## Angiotensin II subtype 1 receptor antagonists

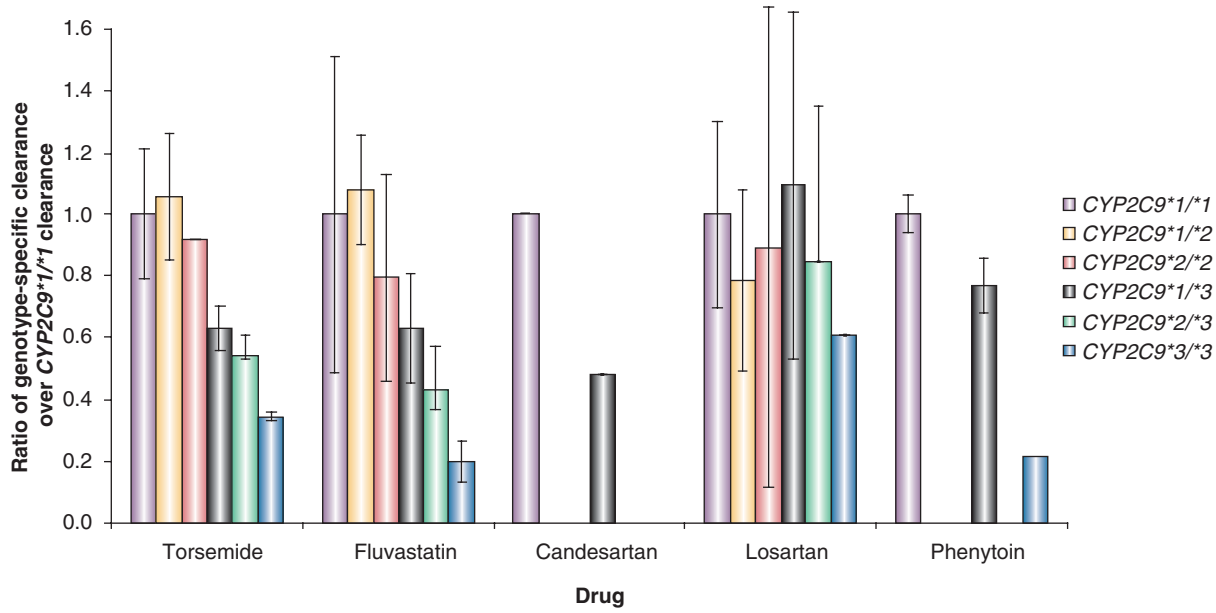
### *Losartan*

Losartan is a prodrug that is metabolized via CYP2C9 to the active and long-acting carboxylic acid metabolite E-3174. Statistically significant differences in losartan and E-3174 kinetics due to the *CYP2C9* genotypes have been reported [87] (Figure 7). Thus, losartan may have a lower efficiency as an antihypertonic agent in carriers of the slow CYP2C9 genotypes, particularly in *3/*3 homozygous individuals. No final clinical study on this assumption has been published and, as such, it is not yet clear whether patients with reduced CYP2C9 activity due to polymorphisms should receive the same dose or a higher dose of losartan or even another angiotensin II subtype 1 receptor antagonist. Indeed, the second Losartan Heart Failure Survival Study (ELITE II) indicated that a number of the patients receiving losartan in the treatment of their heart failure had less than the optimal effect with the standard doses, without adjustment for the *CYP2C9* genotype [88]. As a result many cardiologists now prefer other angiotensin antagonists for heart failure treatment. Further clinical trials that consider the possible impact of CYP2C9 and of the CYP2C9-generated losartan metabolites in the regulation of the vascular tone and inflammation may provide interesting results [89,90].

### *Irbesartan and candesartan*

For irbesartan, which is active itself and has an active CYP2C9-mediated metabolite, Hallberg *et al.* [91] found an enhanced blood pressure reduction in carriers of the *1/*2 and *1/*3 genotypes compared with the *1/*1 genotype. Similarly, candesartan, which is also active itself and has an active metabolite built by CYP2C9, was demonstrated to have an excessive blood pressure reduction in one carrier of the slow-metabolizing *1/*3 genotype [92] (Figure 7, Table 4). However, a comprehensive pharmacokinetic/pharmacodynamic evaluation of the *CYP2C9* polymorphisms in candesartan and irbesartan still remains to be performed.

**Figure 7. Data on the differences in oral clearances of torsemide, fluvastatin, phenytoin and the two angiotensin II subtype 1 receptor antagonists losartan and candesartan due to *CYP2C9* genotypes.**




All data are summarized by calculating weighted means from the specific study's data based on the sample sizes in each of the genotype groups. Standard deviations of the studies were transformed to variation coefficients and are depicted in the figure. References for the studies summarized in this figure are provided in Table 4.

## Other drugs

### *Fluvastatin*

Fluvastatin is a racemate and the (+)-3*R*,5*S*-enantiomer has a 30-fold higher therapeutic activity. About 50–80% of the total fluvastatin oral clearance is mediated by CYP2C9 [93]. Carriers of the *CYP2C9*1/*3* and **3/*3* genotypes displayed mean oral clearances of only 64% (**1/*3*) and 20% (**3/*3*) compared to that measured in wild-type carriers [94]. In contrast to the oral anticoagulants, there was no enantioselectivity or -preference concerning both fluvastatin enantiomers and the *CYP2C9* genotypes. Data from our volunteer study did not indicate *CYP2C9* genotype-related differences in the lipid-lowering effects of fluvastatin. The lacking correlation between genotypes and drug effects might be partially derived from a relatively flat concentration–response curve and from different kinetics of the intrahepatic concentrations (which were not measured), as well as from a contribution of the metabolites to the lipid-lowering effect of this drug. Larger studies in hypercholesteremic patients should evaluate whether there is a difference in efficiency and adverse effects of this drug depending on the CYP2C9 genotypes. Interestingly, fluvastatin, which is a CYP2C9 inhibitor, also appeared to induce vascular CYP2C9 expression [95] and, therefore, vascular CYP2C9 may have substantial physiological roles [89,96]. However, these data are from experimental systems and the probes used may not be absolutely CYP2C9 specific. Thus, further clinical studies are required before one can judge whether or not the *CYP2C9* polymorphisms or the modulation of CYP2C9 expression in the vascular endothelium has any medical relevance beyond drug pharmacokinetics.

### *Phenytoin*

Phenytoin is a prochiral drug that is predominantly metabolized by CYP2C9 with a minor contribution of CYP2C19 [97]. CYP2C9 preferentially catalyzes the formation of the *S*-enantiomer of the metabolite 5-(4-hydroxyphenyl)-5-phenylhydantoin, while CYP2C19 produces the *R*-enantiomer [98,99]. These hydroxylations account for about 90% of the total oral

clearance. Phenytoin is a prototypical drug with nonlinear saturation pharmacokinetics. Therefore, the effect of the *CYP2C9* genotypes might differ depending on the dose administered and, correspondingly, any effects of the genotypes have to be analyzed with the parameters of saturation pharmacokinetics [98,100,101]. These analyses showed that the maximum elimination rate (measured as the pharmacokinetic parameter $V_{maxP}K$) was about 40% lower in carriers of the *CYP2C9*1/*3* genotype compared with **1/*1* carriers, whereas the pharmacokinetic parameter concentration at half maximum elimination rate $K_{mP}K$ (related to the enzyme kinetic parameter $K_m$) was higher in **1/*3* carriers and in carriers of mutant *CYP2C19* alleles compared with the respective wild-type genotypes [82,98,101,102].

In 101 healthy volunteers, after a dose of 300 mg of phenytoin, trough concentrations of the compound were 1.4-fold higher in carriers of one *CYP2C9*3* allele, and 1.3- to 1.6-fold higher in carriers of one or two *CYP2C9*2* alleles compared with the wild type [103]. Correspondingly, in a study in epileptic patients, the mean dosages adjusted by clinical monitoring and by therapeutic drug concentration monitoring differed significantly according to the *CYP2C9* genotype and resulted in about 70% of the standard dose being administered to heterozygous carriers of both the *CYP2C9*3* and **2* alleles compared with the wild type [104].

Case reports on the toxic effects of phenytoin in carriers of *CYP2C9* genotypes that predict low activity support the findings of the clinical studies [105,106]; the first subject to be identified as carring a homozygous *CYP2C9* deletion mutation was a very poor metabolizer of phenytoin [9], with a total clearance of only about 20% compared with the average population. Another case description of a *CYP2C9*3/*3* carrier confirmed this highly reduced oral clearance and emphasized an impressively increased phenytoin elimination half-life of > 100 h compared with an average of 22 h [107].

As a summary for phenytoin, all studies indicated that carriers of the *CYP2C9*1/*3* genotype should receive between 50 and 70% of the standard doses and carriers of the two **3* or **6* alleles should receive about 25% (Figure 7). A similar recommendation was recently derived by Hung *et al.* from a population pharmacokinetic analysis in a Taiwanese sample [102]. These authors recommended a mean daily dose of between 5.5 and 7 mg/kg for carriers of the wild-type allele and a dose of 3–4 mg/kg for carriers of an *CYP2C9*3* allele. Furthermore, they suggested that an even lower dose of 2–3 mg/kg be administered if the *CYP2C9*3* allele occurred in combination with a dysfunctional *CYP2C19* allele.

### *Torsemide*

Torsemide is also known as a CYP2C9 substrate [108]. Intrinsic clearances for *CYP2C9*1* and *CYP2C9*2* catalyzing torsemide methyl hydroxylation were 6.5-fold higher than the intrinsic clearance reported for *CYP2C9*3* (Figure 2). Median torsemide mean oral clearances in carriers of the *CYP2C9*1/*3* and **3/*3* genotypes were reduced to 54 and 34% of the clearances in wild type, respectively, whereas *CYP2C9*2* showed a weaker effect with a total oral clearance of 66% in carriers of the homozygous **2/*2* genotype compared to 100% in **1/*1* individuals [109] (Figure 7). From 0–8 h after torsemide administration, $Na^+$, $K^+$ and $Cl^-$ elimination was higher in carriers of one *CYP2C9*3* allele than in individuals with a homozygous wild-type genotype. In the entire 24-h interval, all CYP2C9-related differences were not statistically significant, with the exception of the decrease in urinary elimination of uric acid in *CYP2C9*3* carriers. *CYP2C9*2* had no effects on urine volume, $Na^+$, $K^+$, $Cl^-$ or uric acid elimination. The differences related to *CYP2C9*3* may warrant further studies, since the involvement of CYP2C9 in endogenous arachidonic acid metabolism may have implications on renal function that are independent of the specific diuretic drug used.

## Environmental modulation of CYP2C9 activity

Besides genetics, a significant fraction of CYP2C9 interindividual variability is due to upregulation by prototypical enzyme inducers, such as rifampin, carbamazapine, or phenobarbital [110,111]. The glucocorticoid receptor, the constitutive androstane receptor and the pregnane X receptor have been identified as mediators of this induction [112,113]. Recent clinical data from our group indicate that rifampin results in approximately a twofold increase of metabolic oral clearance via CYP2C9. A similar induction by a factor of two was seen in all different combinations of *CYP2C9* alleles **1*, **2* and **3* (unpublished data).

In contrast to transcriptional activation stands a CYP2C9 enzyme activation phenomenon exhibited, for instance, by dapsone, which was

**Highlights**

- Pharmacogenetics is claimed to improve drug treatment by enabling the individualization of therapy. Rapid and specific methods for pharmacogenetic analysis are available and *CYP2C9* genotyping in the context of a number of drugs provides an opportunity to utilize pharmacogenetics in clinical practice.
- Genetic factors are known to cause high interindividual variability in drug efficacy and adverse events. However, concise recommendations for selecting therapeutic strategies and dosages based on genotype data are lacking. Specific rules on how to use genotype information is an essential prerequisite for further progress in the clinical application of pharmacogenomic diagnostics.
- The clinical pharmacokinetic effect of the *CYP2C9* polymorphisms *CYP2C9*2* and *CYP2C9*3* can be predicted with reasonable accuracy by *in vitro* incubations with isolated *CYP2C9*1*-, *2- and *3-encoded enzymes. Clinical studies are, however, required to firmly and finally estimate the contribution of CYP2C9 to total drug clearance and for estimation of the pharmacodynamic effects.
- Interpretation of clinical study data on the *CYP2C9* polymorphisms has to consider that CYP2C9 is also involved in the biotransformation of several endogenous arachidonic acid and linoleic acid derivatives, as well as in some reactions in steroid hormones. In addition, extensive linkage within the entire *CYP2C* gene locus (*CYP2C8*, *CYP2C9*, *CYP2C18*, and *CYP2C19*) has to be considered.
- CYP2C9 is involved in the metabolism of frequently used drugs, such as oral hypoglycemics, NSAIDs or oral anticoagulants, and mean total oral clearance differed by up to more than 10-fold between *CYP2C9*1/*1* and *3/*3* genotypes. Such genetically caused differences in pharmacokinetics can be compensated by adjustment of the dosages or dosing intervals. Therefore, knowing and considering the individual *CYP2C9* genotype may increase the safety of many drugs metabolized via CYP2C9.
- Genotype-based individual dosing may improve clinical outcome parameters like survival, days of hospitalization, incidence of severe side effects, and quality of life. This hypothesis derived from observational studies should be proven in prospective studies before pharmacogenetic diagnostics can be used in clinical practice. In a second step, a pharmacoeconomic analysis of CYP2C9 may also be required in order to evaluate reimbursement of the genotyping costs by healthcare organizations.

recently characterized in detail by Hummel *et al.* [114]. Addition of dapsone to the *in vitro* reaction resulted in an increase of intrinsic clearance by 8-fold in the *CYP2C9*1*-encoded enzyme but in an increase of 31- and 47-fold in the *CYP2C9*2*- and *CYP2C9*3*-encoded enzymes, respectively. Thus, dapsone apparently acts differently on the different protein variants. Because of the possible toxicities of dapsone one would not use this drug to decrease genotype-related variability in CYP2C9 activity, but, nevertheless, these data are of great interest for our understanding of the structure–function relationship of the natural CYP2C9 amino acid variants.

While the clinical impact of enzyme activation described above has, to the best of our knowledge, not yet been studied in humans, it is evident that co-medication with enzyme inducers causes significant variability, which may possibly exceed variability due to genotypes. This variability by transcriptional activation acts together with genetic variability and further increases the range of CYP2C9 activities. In other words, if the range of total oral clearance between *CYP2C9*1/*1* versus *3/*3* carriers may be about 6-fold in an uninduced state (Table 4), this range may increase to more than 12-fold if the *1/*1* carrier (but not the *3/*3* carrier) is induced. The effects of genotype and environment have to be considered when selecting between phenotyping and therapeutic drug monitoring versus genotyping for clinical dose adjustments. The current phenotype of a person may be significantly dependent on the current status of enzyme induction, whereas the genotype reflects the lifetime status of a person, but, particularly in the context of multiple medications, this phenotypic information may be preferable to the genotype information.

## Outlook and conclusions

Although *CYP2C9* variants with complete functional deficiency are extremely rare, the frequent polymorphisms in *CYP2C9* do have a substantial impact on drug therapy and knowing the *CYP2C9* genotype might be useful in assigning therapy with oral hypoglycemics, oral anticoagulants, NSAIDs, and some other medications. Data-driven recommendations for dosing of various substrates for individuals carrying the *CYP2C9*2* or *3 alleles have been outlined in this review. The majority of the studies described only evaluated pharmacokinetic and not pharmacodynamic end points but, in clinical practice, the correlations between drug exposure and effect are modulated by multiple other factors. Thus, before routine genotype-guided dosing recommendations can be made for patients, future studies evaluating the influence of genotype on

pharmacokinetics and pharmacodynamics need to be completed, especially prospective studies evaluating such genotype-guided dosing strategies. We believe that the recommendations outlined in this review would certainly be helpful in designing such studies. It is evident that the *CYP2C9* polymorphism would not explain all of the clinical variability. Studies in unselected populations indicated that only 10–20% of variability in drug effects might be explained by *CYP2C9* polymorphisms [137]. But if a fraction of between 10 and 20% of adverse events might really be eliminated by CYP2C9-adjusted dosage, this would be a great advance in medicine.

Due to the enzyme's contribution to endogenous metabolism, *CYP2C9* polymorphisms may have a general medical importance beyond drug therapy. Further biochemical, animal and clinical studies are warranted and may reveal exciting new insights.

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## Website

201. www.imm.ki.se/CYPalleles/CYP2C9.htm *CYP2C9* allele nomenclature.