

CYP2C9: warfarin

5771-5777

*1 = no CYP2C9 gene variant, normal activity, *2 = CYP2C9 gene variant with decreased activity, *3 = CYP2C9 gene variant with strongly decreased activity, 95% CI = 95% confidence interval, HR = hazard ratio, IM = IM OTHER = intermediate metaboliser, other genotype (decreased CYP2C9 enzyme activity due to a gene variant with decreased activity other than *2 or *3), INR = international normalised ratio, NM = normal metaboliser (*1/*1) (normal CYP2C9 enzyme activity), NS = not significant, OR = odds ratio, PM = PM OTHER = poor metaboliser, other genotype (strongly decreased CYP2C9 enzyme activity due to the presence of two gene variants with decreased activity, of which at least one other than *2 or *3), RR = risk ratio, S = significant, VKA = vitamin K antagonist, VKORC1 = vitamin K epoxide reductase, subunit 1

Disclaimer: The KNMP Pharmacogenetics Working Group formulates optimal drug recommendations based on the available evidence. If these optimal recommendations cannot be followed due to practical restrictions, e.g. because therapeutic drug monitoring or lower doses are not available, health care professionals should consider the next best option.

Concise summary and justification of choices:

The most potent enantiomer of warfarin, S-warfarin, is predominantly metabolised into inactive metabolites by CYP2C9. Gene variants leading to an enzyme with reduced activity might therefore diminish the dose required. This was confirmed by eight meta-analyses investigating the association between warfarin dose and gene variants with reduced activity (Asiimwe 2024, Zhang 2024, Asiimwe 2020, Takeuchi 2020, Zhang 2016, Jorgensen 2012, Lindh 2009, and Sanderson 2005).

Three meta-analyses found an increased bleeding risk in patients with one or two alleles with reduced activity (Zhang 2024, Yang 2013, and Sanderson 2005). For the separate genotypes, a significantly increased bleeding risk was only found for *1/*3 and *3/*3 in one meta-analysis, and only for *3/*3 in another meta-analysis (Yang 2013 and Jorgensen 2012). For the other genotypes, Yang 2013 only found a significant effect after grouping them with other genotypes. As expected based on predicted enzyme activity, Lindh 2009 found a larger dose reduction for *2/*3 than for *1/*3. Both Lindh 2009 and Jorgensen 2012 found a similar dose reduction for *2/*2 as for *1/*3. Based on these results, it can be expected that also *2/*2 and *2/*3 lead to an enhanced bleeding risk. For this reason, for these four genotypes, the KNMP Pharmacogenetics Working Group concluded that the gene-drug interaction leads to the necessity to adjust therapy by using lower initial doses (yes/yes-interactions).

For *1/*2, there is only evidence of an increased bleeding risk when analysed together with genotypes with a stronger reduced CYP2C9 activity. In addition, the required dose reduction is small (approximately 20%, which is 1.5 times smaller than the required dose reduction for *1/*3 and *2/*2). Therefore, if *1/*2 has an increased bleeding risk, the increase in risk is probably small. For this reason, the KNMP Pharmacogenetics Working Group considered the evidence insufficient to recommend therapy adjustment for this genotype-drug interaction (yes/no-interaction).

For IM and PM, a meta-analysis of 6 genome-wide association studies showed a lower required dose in carriers of the *8-allele, and another meta-analysis showed a lower required dose for *1/*5, *1/*8, and *1/*11 (Asiimwe 2024, and Asiimwe 2020). Because Asiimwe 2020 showed the dose reduction in *1/*5 to be similar to that in *1/*3, and because the *6 allele has no activity, IM and PM include genotypes with an effect size equal to or larger than *1/*3 and *3/*3. Therefore, also for these genotypes, the KNMP Pharmacogenetics Working Group decided to recommend lowering of the initial doses (yes/yes-interactions).

You can find an overview of the effects per genotype in the background information text of the corresponding genotype-drug interaction in the KNMP Kennisbank. You might also have access to this background information text via your pharmacy or physician electronic decision support system.

The justification of the therapeutic recommendations and a note on the meta-analyses comparing genotype-guided with non-genotype-guided dosing you will find below.

Therapeutic recommendations

Dose reductions are derived from the meta-analysis of Lindh 2009. This is the largest meta-analysis on the effect of CYP2C9 genotype on dose. To facilitate the use, the recommended percentages of the normal initial doses are rounded off to multiples of 5%. For IM and PM, to avoid overanticoagulation, it was decided to recommend the largest dose reduction observed for the *2- and *3-alleles, i.e. the dose reduction for *1/*3 and *3/*3.

Because a reduced metabolism is associated with a longer half-life, it is associated with a longer time to steady state concentrations. For this reason, a warning for a longer time to steady state is included for the genotype-warfarin combinations with a recommendation to decrease the dose to less than 50% of the normal dose.

Note

Two meta-analyses of studies comparing genotype-guided with not genotype-guided dosing showed a genotype-guided treatment to reduce the risk of bleeding events (OR = 0,24 and RR = 0,82) (Wang 2019 and Tse 2018). One of these showed genotype-guided treatment also to reduce the risk of adverse events (OR = 0,60), while the chance of receiving a warfarin-stable therapeutic dose during follow-up was increased (OR = 2,68) (Wang 2019). The other showed genotype-guided treatment also to reduce the risk of INR \geq 4 (Tse 2018). Another meta-analysis showed genotype-guided treatment to reduce the incidence of major bleeding (Franchini 2014). However, a meta-analysis investigating the same 7 trials, but not excluding a trial with zero incidences of major bleeding did not (Stergiopoulos 2014). The network meta-analysis of Sridharan 2021 did not show an effect on bleeding risk for therapy guided by both CYP2C9 and VKORC1 genotypes, but showed a reduced bleeding risk for therapy guided by CYP2C9 genotype only (OR = 0.30). Two other meta-analyses showed little or no improvement of clinical outcomes by genotype-guided dosing (Liao 2015 and Xu 2014). However, these studies considered only data for the whole group, including the patients without variant alleles. The absence of an effect for the whole group does not preclude an effect for the patients with the expected most benefit of genotype-guided dosing, i.e. the patients with variant alleles. In addition, in several of the included studies the initial dose was fixed and not genotype-guided. In patients with known genotypes, also the initial dose can be adapted.

Recommendation concerning pre-emptive genotyping, including justification of choices:

The KNMP Pharmacogenetics Working Group considers genotyping before starting warfarin to be beneficial for drug safety. It is advised to consider genotyping the patient before (or directly after) drug therapy has been initiated to guide dose selection.

The clinical implication of the gene-drug interaction scores 5 out of the maximum of 10 points (with pre-emptive genotyping considered to be beneficial for scores ranging from 3 to 5 points) (see also the clinical implication score tables at the end of this risk analysis):

The only meta-analysis investigating major bleeding (severity code D corresponding to CTCAE grade 3) found a significantly higher incidence in patients with a CYP2C9 gene variant (Yang 2013). This results in 1 out of the maximum of 2 points for the first criterion of the clinical implication score, the clinical effect associated with the gene-drug interaction (1 point for CTCAE grade 3 or 4).

A clinical effect grade \geq 3 was only found in the meta-analyses of Yang 2013. This results in 1 out of the maximum of 3 points for the second criterion of the clinical implication score, the level of evidence supporting an associated clinical effect grade \geq 3 (1 point for one publication with level of evidence score \geq 3).

The meta-analysis for major bleeding included 3 studies in non-Saudi Whites (Yang 2013). The incidence of major bleeding in *1/*1 and (*2- and/or *3-carriers) in these 3 studies was 9.9% and 18.9%, respectively, while 25.9% of the patients in these studies were (*2 and/or *3 carriers). So, the absolute risk increase in (*2 and/or *3 carriers) was 9%. This indicates that if adjusting warfarin therapy based on genotype could prevent all excess major bleeding events in patients with a CYP2C9 gene variant, it would prevent major bleeding in 9% of these patients. Because the prevalence of patients with a CYP2C9 gene variant was 25.9%, it would prevent major bleeding in $9 \times 0,259 = 2.3\%$ of all patients. This corresponds to a number needed to genotype to prevent one event of major bleeding of 43. This results in 2 out of the maximum of 3 points for the third criterion of the clinical implication score, the number needed to genotype (NNG) to prevent one clinical effect grade \geq 3 (2 points for $10 \leq$ NNG \leq 100).

There is no Dutch Summary of Product Characteristics (SmPC) of warfarin. The American SmPC mentions CYP2C9 *1/*2, *1/*3, *2/*2, *2/*3, and *3/*3, but does not mention these genotypes as a contra-indication and does not recommend to genotype CYP2C9. This results in 1 out of the maximum of 2 points for the fourth and last criterion of the clinical implication score, the pharmacogenetics information in the SmPC (1 point for at least one genotype/phenotype mentioned in the SmPC, but no genotype/phenotype mentioned as a contra-indication and no recommendation to genotype).

The table below follows the KNMP definition for IM and PM (i.e. only IM OTHER and PM OTHER). The definition used in the table below may therefore differ from the definition used by the authors in the article.

Source	Code	Effect	Comments
ref. 1 Asiimwe IG et al. Meta-analysis of genome-wide association studies of stable warfarin dose in patients of African ancestry. Blood Adv 2024;8:5248-61. PMID: 39163621.	3	Meta-analysis of 6 genome-wide association studies of stable warfarin dose in African and African American cohorts. The meta-analysis included a total of 989 African and 515 African American patients. The mean proportion of African ancestry in the included patients was 86,1%. Part of the single nucleotide polymorphisms were imputed. For all cohorts, multivariable linear regression was undertaken assuming an additive mode of inheritance and adjustment for 5 nongenetic covariates (age, sex, weight, target INR range, and simvastatin/amiodarone status) and 10 principal components of genetic ancestry. Standard error-weighted meta-analyses with genomic control correction using METAL were performed. The protocol (including statistical analysis) was not prospec-	Author's conclusion: 'We reaffirmed the importance of CYP2C9 and VKORC1 in influencing warfarin dose requirements.'

<p>ref. 1, continuation</p>	<p>IM+PM: A</p>	<p>tively registered. In addition, it is not explained why the 6 included cohorts were chosen. Neither is a systemic quality analysis of the cohorts performed.</p> <p>The genome-wide association studies were not published previously. However, the cohorts were, but there was no bias analysis for the cohort studies.</p> <p>With a total sample size of 1504 and assuming an additive genetic mode of inheritance, a standard deviation of stable warfarin dose of 2.66 mg/d, a minimal difference in stable dose requirements of 1 mg/d to be clinically important, and a genome-wide significance threshold of 5×10^{-8}, study power was computed as 17.3%, 78.1%, 97.6%, and 99.8% for single nucleotide polymorphisms with frequencies of 5%, 10%, 15%, and 20%, respectively.</p> <p>Results:</p> <ul style="list-style-type: none"> - The strongest associations were found with single nucleotide polymorphisms (SNPs) on chromosome 16 (VKORC1 locus) and chromosome 10 (CYP2C loci). If only patients with African ancestry were included, the associations with SNPs on chromosome 10 became stronger than with those on chromosome 16. - The only genome-wide significant association within the CYP2C9 locus was with CYP2C9 *8, both in all patients and in the patients with African ancestry. It led to a decrease in warfarin dose with 34% in all patients and with 31% in patients with African ancestry. Heterogeneity between the cohorts was absent for patients with African ancestry and low to moderate ($I^2 = 36.8\%$) for all patients. 													
<p>ref. 2 Zhang S et al. Association between CYP2C9 and VKORC1 genetic polymorphisms and efficacy and safety of warfarin in Chinese patients. Pharmacogenet Genomics 2024;34:105-16. PMID: 38470454.</p>	<p>3</p> <p>*1/*3+ *3/*3: C</p>	<p>Meta-analyses of 22 studies. The meta-analysis for warfarin dose included 16 studies (with a total of 240 *1/*3 and 3238 *1/*1) and those for bleeding risk 8 studies (with a total of 291 *1/*3+*3/*3 and 1762 *1/*1).</p> <p>Bleeding events occurred in 17.5% of patients in the meta-analysis.</p> <p>Meta-analyses were performed with a random-effects model in case of heterogeneity between the studies and with a fixed-effect model in the absence of heterogeneity. This indicates that the statistical method was chosen afterwards. The search and selection strategy was transparent, but the data extraction was not described.</p> <p>Quality of the included studies was assessed with the Cochrane methodology. However, this method is meant for randomised controlled trials and not for cohort studies. In addition, the result was not reported per study and the result was not reported for studies in the CYP2C9 and VKORC1 meta-analyses separately.</p> <p>Publication bias analysis was not performed.</p> <p>Results:</p> <table border="1" data-bbox="531 1615 1238 1832"> <tr> <td colspan="3">Results compared to *1/*1:</td> </tr> <tr> <td>mean difference in dose (in mg/ day)</td> <td>*1/*3</td> <td>-1.09 (95% CI: -0.99 – -1.20) (S)</td> </tr> <tr> <td>bleeding</td> <td>*1/*3+*3/*3</td> <td>OR = 2.60 (95% CI: 1.93-3.51) (S)</td> </tr> <tr> <td colspan="3">Heterogeneity between the studies was insignificant for both meta-analyses.</td> </tr> </table>	Results compared to *1/*1:			mean difference in dose (in mg/ day)	*1/*3	-1.09 (95% CI: -0.99 – -1.20) (S)	bleeding	*1/*3+*3/*3	OR = 2.60 (95% CI: 1.93-3.51) (S)	Heterogeneity between the studies was insignificant for both meta-analyses.			<p>Author's conclusion: 'A meta-analysis conducted to consolidate findings confirmed the associations of both CYP2C9 (rs1057910) and VKORC1 (rs9923231) with stable warfarin dosage. Notably, CYP2C9 variant genotypes were significantly linked to an increased risk of hemorrhagic complications, VKORC1 did not demonstrate a similar association.'</p>
Results compared to *1/*1:															
mean difference in dose (in mg/ day)	*1/*3	-1.09 (95% CI: -0.99 – -1.20) (S)													
bleeding	*1/*3+*3/*3	OR = 2.60 (95% CI: 1.93-3.51) (S)													
Heterogeneity between the studies was insignificant for both meta-analyses.															
<p>ref. 3 Sridharan K et al. A network meta-analysis of CYP2C9, CYP2C9 with VKORC1 and CYP2C9 with VKORC1 and CYP4F2 genotype-based warfarin dosing stra-</p>	<p>4</p>	<p>Network meta-analysis of 26 randomized controlled trials with 7898 patients comparing genotype-guided dosing with not genotype-guided dosing. Genotype-guided dosing was based on CYP2C9 genotype only in 2 of the included trials, on both CYP2C9 and VKORC1 genotype in 5 trials, and on CYP2C9, VKORC1 and CYP4F2 genotypes in 19 trials.</p> <p>The follow-up duration varied from 2-4 weeks to 6 months. In 16 trials, initial dose in the not-genotype-guided group was fixed. In 6 trials, it was based on a clinical algorithm. In</p>	<p>Author's conclusion: 'The present evidence is supportive of personalizing warfarin dose based only on CYP2C9 and VKORC1 geno-</p>												

<p>tegies compared to traditional. J Clin Pharm Ther 2021;46:640-8. PMID: 33346393.</p> <p>ref. 3, continuation</p>	<p>1 trial, it was fixed in one group and based on a clinical algorithm in the other group. In the remaining 3 trials, it was not specified. The therapeutic INR range differed between the trials.</p> <p>Network meta-analysis permits the evaluation of more than two groups of interventions simultaneously. Trial sequential analysis was carried out for the outcomes associated with CYP2C9 and VKORC1 only, because of the low number of studies for the other genotype combinations. For time to first therapeutic INR, the meta-analysis included 8 trials with a total of 1843 patients, of which 7 with a total of 1652 patients for VKORC1 and CYP2C9 and 1 with 191 patients for CYP2C9. For time to stable INR/warfarin dose, the meta-analysis included 12 trials with a total of 2260 patients, of which 8 with a total of 1480 patients for CYP2C9 and VKORC1, 3 with a total of 589 patients for VKORC1, CYP2C9 and CYP4F2, and 1 with 191 patients for CYP2C9. For percentage of time in therapeutic range, the meta-analysis included 18 trials with a total of 6356 patients, of which 4 with a total of 4249 patients for CYP2C9 and VKORC1, 13 with a total of 2069 patients for VKORC1, CYP2C9 and CYP4F2, and 1 with 38 patients for CYP2C9. For time to first supratherapeutic INR, the meta-analysis included 3 trials with a total of 451 patients, of which 2 with a total of 226 patients for CYP2C9 and VKORC1, and 1 with 225 patients for VKORC1, CYP2C9 and CYP4F2. For proportion of patients with supratherapeutic anticoagulation, the meta-analysis included 17 trials with a total of 6095 patients, of which 13 with a total of 4079 patients for CYP2C9 and VKORC1, 3 with a total of 1978 patients for VKORC1, CYP2C9 and CYP4F2, and 1 with 38 patients for CYP2C9. For bleeding risk, the meta-analysis included 16 trials with a total of 6246 patients, of which 11 with a total of 3994 patients for CYP2C9 and VKORC1, 3 with a total of 2023 patients for VKORC1, CYP2C9 and CYP4F2, and 2 with a total of 229 patients for CYP2C9. For risk of thromboembolic episodes, the meta-analysis included 8 trials with a total of 3636 patients, of which 4 with a total of 1575 patients for CYP2C9 and VKORC1, 3 with a total of 2023 patients for VKORC1, CYP2C9 and CYP4F2, and 1 with 38 patients for CYP2C9. For mortality, the meta-analysis included 4 trials with a total of 2000 patients, of which 3 with a total of 1775 patients for CYP2C9 and VKORC1, and 1 with 225 patients for VKORC1, CYP2C9 and CYP4F2.</p> <p>Quality of the included trials was assessed with the Cochrane Risk Assessment Tool. The risk of bias in seven domains was assessed: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome data, selective reporting, and other bias. Of the 26 included trials, 5 had a low risk of bias in all 7 domains, 1 had a low risk in 5 domains and an unclear risk in 2 domains (random sequence generation and allocation concealment), 6 had a low risk of bias in 6 domains and a high risk in 1 domain (blinding of outcome assessment in 5 trials and blinding of participants and personnel in 1 trial), 3 had a low risk in 4 domains, an unclear risk in 2 domains (random sequence generation and allocation concealment in 2 trials and blinding of participants and personnel and blinding of outcome assessment in 1 trial) and a high risk in 1 domain (blinding of outcome assessment in 2 trials and allocation concealment in 1 trial), 4 had a low risk in 5 domains and a high risk in 2 domains (blinding of outcome assessment in all 4 trials, and blinding of participants and personnel in 2 trials, random sequence generation in 1 trial, and allocation</p>	<p>types compared to traditional strategies. No convincing evidence exists supporting the role of CYP2C9 alone.'</p>
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ref. 3, continuation

concealment in 1 trial), 1 had a low risk in 4 domains, an unclear risk in 1 domain (random sequence generation) and a high risk in 2 domains (blinding of participants and personnel and blinding of outcome assessment), 2 had a low risk in 3 domains, an unclear risk in 2 domains (blinding of participants and personnel and blinding of outcome assessment) and a high risk in 2 domains (random sequence generation and allocation concealment), 1 had a low risk in 2 domains, an unclear risk in 3 domains (allocation concealment, selective reporting, and other bias) and a high risk in 2 domains (blinding of participants and personnel and blinding of outcome assessment), 3 had a low risk in 4 domains and a high risk in 3 domains (random sequence generation, allocation concealment, and blinding of outcome assessment), and 1 had a low risk in 3 domains and a high risk in 4 domains (random sequence generation, allocation concealment, blinding of participants and personnel, and blinding of outcome assessment). The authors indicate that a low risk of bias was observed in most of the domains. 2 of the included trials were published as conference abstracts only.

Meta-analyses were performed with a random-effects model, indicating that the statistical method was chosen prospectively, but prospective registration of the study protocol was not mentioned. The search and selection strategy was transparent, and the data extraction was standardised.

Publication bias analysis was performed with funnel plots and Egger's tests, but only for at least five studies, i.e. only for VKORC1 + CYP2C9.

Results:

Genotype-guided in comparison with not-genotype-guided therapy (direct comparison pooled estimates):		
	genotype-guided therapy	
time to first therapeutic INR	VKORC1 + CYP2C9	Weighted mean difference = -1.92 days (95% CI: -0.61 – -3.23) (S) Trial sequential analysis confirmed that VKORC1 + CYP2C9 is associated with a shorter time to first therapeutic INR. Based on the GRADE classification, the quality of the evidence for time to first therapeutic INR with VKORC1 + CYP2C9 was “moderate”. Studies with high risk of bias were included.
	CYP2C9	Weighted mean difference = -2.73 days (95% CI: -2.05 – -3.41) (S) Based on the GRADE classification, the quality of the evidence for time to first therapeutic INR with CYP2C9 was “low”. Studies with high risk of bias were included and publication bias could not be assessed/ruled out.
	VKORC1 + CYP2C9	Weighted mean difference = -4.60 days (95% CI: -2.34 – -6.87) (S) Results were similar for the subgroup of Whites: weighted mean difference = -3.90 days (95% CI: -3.76 – -4.04) (S)
time to stable INR/warfarin dose	VKORC1 + CYP2C9	Weighted mean difference = -4.60 days (95% CI: -2.34 – -6.87) (S) Results were similar for the subgroup of Whites: weighted mean difference = -3.90 days (95% CI: -3.76 – -4.04) (S)

ref. 3, continuation				Results were similar after excluding data from conference abstracts: weighted mean difference = -5.18 days (95% CI: -2.14 – -8.22) (S)	
				Trial sequential analysis confirmed that VKORC1 + CYP2C9 is associated with a shorter time to stable INR/warfarin dose.	
				No significant differences were observed for VKORC1 + CYP2C9 compared to CYP2C9.	
				Based on the GRADE classification, the quality of the evidence for time to stable INR/warfarin dose with VKORC1 + CYP2C9 was “very low”. Studies with high risk of bias were included, publication bias could not be assessed/ruled out, and limitations in the precision of the estimates were serious.	
			VKOR-C1 + CYP-2C9 + CYP4F2	NS	
				Results were also NS for the subgroup of Whites.	
				Results were also NS after excluding data from conference abstracts.	
			CYP-2C9	CYP2C9, VKORC1 and CYP4F2 were associated with a longer time to stable INR/warfarin dose compared to CYP2C9 (weighted mean difference = 6.52 days (95% CI: 1.32-11.72) (S))	
				Weighted mean difference = -8.10 days (95% CI: -3.66 – -12.54) (S)	
				Results were similar after excluding data from conference abstracts: weighted mean difference = -8.10 days (95% CI: -3.66 – -12.54) (S)	
			% of time in therapeutic range	VKOR-C1 + CYP-2C9	Weighted mean difference = 3.91% (95% CI: 1.18-6.63) (S)
					Results were similar for the subgroup of Whites: weighted mean difference = 4.55% (95% CI: 0.61-8.49) (S)
Trial sequential analysis confirmed that VKORC1 + CYP2C9 is associated with a higher % of time in therapeutic range.					
Based on the GRADE classification, the quality of the evidence for percentage of time in therapeutic range with VKORC1 + CYP2C9					

ref. 3, continuation			was “very low”. Studies with high risk of bias were included, publication bias could not be assessed/ruled out, and limitations in the precision of the estimates were serious.
		VKOR-C1 + CYP-2C9 + CYP4F2	NS Results were also NS for the subgroup of Whites.
		CYP-2C9	NS Results were also NS for the subgroup of Whites.
	time to first supra-therapeutic INR	VKOR-C1 + CYP-2C9	NS Trial sequential analysis confirmed that the present evidence is inconclusive about a possible association of VKORC1 + CYP2C9 with time to first supratherapeutic INR.
		VKOR-C1 + CYP-2C9 + CYP4F2	NS
	proportion of patients with supra-therapeutic anti-coagulation	VKOR-C1 + CYP-2C9	NS Results were also NS for the subgroup of Whites.
			Results were also NS after excluding data from conference abstracts.
			Trial sequential analysis confirmed that the present evidence is inconclusive about a possible association of VKORC1 + CYP2C9 with proportion of patients with supra-therapeutic anticoagulation.
		VKOR-C1 + CYP-2C9 + CYP4F2	OR = 0.68 (95% CI: 0.49-0.93) (S)
			Results were similar for the subgroup of Whites: OR = 0.69 (95% CI: 0.48-0.99) (S)
			Results were similar after excluding data from conference abstracts: OR = 0.68 (95% CI: 0.49-0.93) (S) Based on the GRADE classification, the quality of the evidence for proportion of patients with supra-therapeutic anticoagulation with VKORC1 + CYP2C9 + CYP4F2 was “moderate”. Studies with high risk of bias were included.
	CYP-2C9	NS Results were also NS for the subgroup of Whites.	
		Results were also NS after excluding data from conference abstracts.	
	bleeding risk	VKOR-C1 + CYP-2C9	NS Results were also NS for the subgroup of Whites.
			Results were also NS after excluding data from conference

ref. 3, continuation	geno- type- guided versus not geno- type- guided therapy: AA#			abstracts.			
						Trial sequential analysis confirmed that the present evidence is inconclusive about a possible association of VKORC1 + CYP2C9 with bleeding risk.	
				VKOR-C1 + CYP-2C9 + CYP4F2		NS	
						Results were also NS for the subgroup of Whites.	
						Results were also NS after excluding data from conference abstracts.	
				CYP-2C9		OR = 0.30 (95% CI: 0.10-0.86) (S)	
						Results were NS for the subgroup of Whites.	
						Results were similar after excluding data from conference abstracts: OR = 0.30 (95% CI: 0.10-0.86) (S)	
				risk of thromboembolic episodes		VKOR-C1 + CYP-2C9	NS
							Results were also NS for the subgroup of Whites.
						VKOR-C1 + CYP-2C9 + CYP4F2	NS
							Results were also NS for the subgroup of Whites.
						CYP-2C9	NS
							Results were also NS for the subgroup of Whites.
				mortality		VKOR-C1 + CYP-2C9	NS
	VKOR-C1 + CYP-2C9 + CYP4F2	NS					
Results were similar for mixed treatment comparison estimates.							
Publication bias was present for VKORC1 + CYP2C9 for the outcomes: - time to stable INR/warfarin dose - percentage of time in therapeutic range - bleeding risk There were no indications for publication bias for VKOR-C1 + CYP2C9 for the outcomes: - time to first therapeutic INR - proportion of patients with supratherapeutic INR Publication bias analysis was not performed for the other comparisons.							
ref. 4 Asiimwe IG et al. Genetic factors influencing warfarin dose in Black-African patients: A systematic review and meta-analysis. Clin Pharmacol Ther 2020; 107:1420-33.	3	Meta-analysis of data on Black-African patients derived from 14 studies with at least 5% of Black-African patients. The meta-analysis for *2-heterozygotes included 2054 patients without *2 and 139 *2-heterozygotes derived from 13 studies. The meta-analysis for *3-heterozygotes included 1706 patients without *3 and 48 *3-heterozygotes derived from 9 studies. The meta-analysis for *5-heterozygotes included 1277 patients without *5 and 20 *5-heterozygotes derived from 6 studies. The meta-analysis for *8-heterozygotes included 821 patients without *8 and 97 *8-		Author's conclusion: 'Significant predictors for CYP2C9 and stable dose included rs1799853 (CYP2C9*2), rs1057910 (CYP2C9*3),			

PMID: 31869433.

ref. 4, continuation

heterozygotes derived from 7 studies. The meta-analysis for *11-heterozygotes included 1474 patients without *11 and 35 *11-heterozygotes derived from 7 studies. Heterozygotes of an allele were defined as any combination of the allele with another allele, so not only as the combination of the allele with *1. Of the included studies, 8 were performed in the USA, 1 in Puerto Rico and the USA, 2 in Brazil, 2 in South Africa, and 1 in Sudan. Studies differed in the target INR. Methodological quality of the included studies was assessed qualitatively by applying the check-list of Jorgensen and Williams (containing questions on 10 domains: choosing the genes/SNPs to genotype (6 questions), sample size (4 questions), study design (3 questions), reliability of genotypes (7 questions), missing genotype data (6 questions), population stratification (3 questions), Hardy-Weinberg equilibrium (5 questions), mode of inheritance (4 questions), choice and definition of outcomes (3 questions), and compliance to treatment (2 questions)). The authors concluded that whilst many issues of concern were raised in terms of the methodological quality, no studies stood out in terms of being of particularly low quality overall.

Standard meta-analysis was performed for alleles other than *8. For *8, which was the only allele for which part of the studies included homozygotes of the variant (*8/*8), meta-analyses were performed with a genetic model-free approach. For this approach, variant homozygotes were imputed in the 2 studies without homozygotes, with the imputation based on the 5 studies with one or more homozygotes. For this reason, the meta-analysis for the *8/*8 homozygotes is partly (for 15%, 2 imputed *8/*8 and 11 not imputed *8/*8) based on imputed instead of observed data. That is why we decided not to include this meta-analysis in this abstract.

The review protocol was registered prospectively in PROSPERO. However, except for *8-heterozygotes, meta-analyses were performed with a random-effects model in case of substantial heterogeneity between the studies and with a fixed-effect model in the case of low heterogeneity. This indicates that the statistical method was chosen afterwards. The search and selection strategy was transparent and the data extraction was standardised.

Publication bias analysis was performed with linear regression test of funnel plot asymmetry, but only for meta-analysis including more than 10 studies, so only for the meta-analysis of *2-heterozygotes.

None of the 14 studies in this meta-analysis were included in the meta-analysis of Zhang 2024.

rs28371686 (CYP2C9*5), rs9332131 (CYP2C9*6), and rs28371685 (CYP2C9*11) reducing dose by 6.8, 12.5, 13.4, 8.1, and 5.3 mg/week respectively.'

4 *1/*2: A
*1/*3: A
IM: A

Results:

Dose for heterozygous for the allele compared to no allele:		
allele	mean difference (in mg/week)	95% CI
*2	-6.75	-4.59 – -8.91
*3	-12.51	-6.83 – -18.18
*5	-13.38	-10.07 – -16.68
*8	NS	
Results were significant if meta-analysis was performed in the same way as for the other alleles (i.e. by standard pairwise comparison instead of a genetic-model-free approach): mean difference = -6.42 (95% CI: -3.31 – -19.54) mg/week.		
*11	-5.31	-0.43 – -10.18

<p>ref. 4, continuation</p>		<p>The heterogeneity between the studies was substantial and significant for *3-heterozygotes. The heterogeneity between the studies was absent or low and not significant for the other meta-analyses. Note: Despite the absence of heterogeneity between the studies for *8-heterozygotes, a random-effects model instead of a fixed effects model was used for the meta-analysis performed by the genetic model-free approach.</p> <p>Based on the Venice interim criteria, the quality of the evidence for the effect on warfarin dose was “moderate” for each of the alleles.</p> <p>There was no evidence of publication bias for *2-heterozygotes (linear regression test of funnel plot asymmetry p-value = 0.85).</p> <p>Except for the *11-heterozygotes, results were similar if heterozygotes for an allele were defined as *1 combined with this allele and if no allele was defined as *1/*1 (pairwise comparison for *8-heterozygotes). For *11-heterozygotes, the number of studies in the meta-analysis decreased to 4 and the result lost significance.</p> <p>Except for the *11-heterozygotes, in which case significance was lost, results were similar in secondary meta-analyses in which eligible International Warfarin Pharmacogenetics Consortium (IWPC) study sites were included (while excluding all studies whose population came from a site that was part of IWPC to avoid duplication). IWPC was a secondary study and it was not possible to assess the methodological quality of the IWPC datasets.</p> <p>The authors indicate that the results for *2 and *3 are similar to those previously observed in White patients.</p> <p>NOTE: Results for *6- and *9-heterozygotes (meta-analyses of less than 5 studies) and *8/*8 (for 2 of the 13 *8/*8 based on imputed instead of observed data or, in pairwise comparison, only 5 studies contributing *8/*8 patients) are not included in the abstract.</p>	
<p>ref. 5 Takeuchi M et al. CYP2C9, VKORC1, and CYP4F2 polymorphisms and pediatric warfarin maintenance dose: a systematic review and meta-analysis. Pharmacogenomics J 2020;20:306-319. PMID: 31673144.</p>	<p>3</p>	<p>Meta-analysis of 8 studies in children with a total of 157 *1/*2+*1/*3 and 342 *1/*1. Doses in mg/kg per day were available in 7 studies with a total of 149 *1/*2+*1/*3 and 320 *1/*1. Homozygotes for variant alleles were present in 4 studies with a total of 39 *2/*2+*2/*3+*3/*3 and 165 *1/*1. Doses in mg/kg per day were available in 3 of these studies with a total of 19 *2/*2+*2/*3+*3/*3 and 143 *1/*1. Studies differed in the included age ranges and median ages. Median target INR in the studies varied from 1.6 to 2.7. In 6 of the 8 included studies, most patients were Whites. Of the included studies, 3 scored the maximum of 9 points on the Newcastle-Ottawa Scale, 2 scored 8 points, and 3 scored 7 points. This indicates that all included studies were of high quality (score of 7 or higher). In addition, one of the included studies scored 21 of the maximum of 24 points on the Strengthening the Reporting of Genetic Association studies (STREGA) statement, 2 scored 20 points, 1 scored 18 points, 3 scored 17 points, and 1 scored 13 points. STREGA contains 12 items associated with valid data reported in the study. For each item, “yes” is scored 2, “unknown” is scored 1, and “no” is scored 0. A total score over 16 of the maximum of 24 points was arbitrarily defined as high quality. So, according to this, 7 out of 8 of the included studies were of high quality. Warfarin maintenance dose was defined as the dose required to achieve three consecutive INR measurements within the target therapeutic range over a minimum of 4</p>	<p>Author’s conclusion: ‘Our meta-analysis provides evidence that CYP2C9 and VKORC1 variant statuses affect warfarin maintenance dose in children, but not CYP4F2.’</p>

<p>ref. 5, continuation</p>	<p>*1/*2+ *1/*3: A</p> <p>*2/*2+ *2/*3+ *3/*3: A</p>	<p>weeks.</p> <p>Because weight-adjusted doses in mg/kg/day were unavailable in 1 of the included studies, the standardized mean difference (SMD) of the warfarin doses was calculated for the meta-analysis of all 8 studies, i.e. the mean differences (MD) of the doses (mg/day) divided by the pooled standard deviation. The SMD expresses the size of the effect in each study relative to the variability observed in that study, allowing a direct comparison of the effect of the gene polymorphisms across trials that used different scales. The magnitude of the effect size represented by the SMD was interpreted as follows: small, if the absolute value of the SMD was <0.4; moderate, if it was between 0.4 and 0.7; and large, if >0.7.</p> <p>The review protocol was registered prospectively in PROSPERO. Meta-analyses were performed with a random-effects model. The search and selection strategy was transparent and the data extraction was standardised. Publication bias analysis was performed with funnel plots, but only for the comparison of *1/*2+*1/*3+*2/*2+*2/*3+*3/*3 with *1/*1, not for the comparisons of *1/*2+*1/*3 with *1/*1 and *2/*2+*2/*3+*3/*3 with *1/*1. There were no indications for publication bias for the comparison of *1/*2+*1/*3+*2/*2+*2/*3+*3/*3 with *1/*1.</p> <p>Results:</p> <table border="1" data-bbox="531 869 1233 1395"> <thead> <tr> <th colspan="3">Dose compared to *1/*1:</th> </tr> <tr> <th></th> <th>standardized mean difference</th> <th>95% CI</th> </tr> </thead> <tbody> <tr> <td>*1/*2+*1/*3</td> <td>-0.512</td> <td>-0.311 – -0.713</td> </tr> <tr> <td colspan="3">This indicates a moderate effect on the dose.</td> </tr> <tr> <td>*2/*2+*2/*3+*3/*3</td> <td>-1.099</td> <td>-0.670 – -1.528</td> </tr> <tr> <td colspan="3">This indicates a large effect on the dose.</td> </tr> </tbody> </table> <p>Heterogeneity between the studies was absent for both comparisons.</p> <p>Exclusion of the low-quality study did not change the findings, which indicates that the results of the analysis were stable.</p> <p>Based on the GRADE classification, the quality of the evidence for the effect of CYP2C9 on warfarin maintenance dose was “high”.</p> <table border="1" data-bbox="531 1429 1233 1563"> <thead> <tr> <th colspan="3">Daily dose compared to *1/*1:</th> </tr> <tr> <th></th> <th>mean difference</th> <th>95% CI</th> </tr> </thead> <tbody> <tr> <td>*1/*2+*1/*3</td> <td>-0.033 mg/kg</td> <td>-0.019 – -0.047</td> </tr> <tr> <td>*2/*2+*2/*3+*3/*3</td> <td>-0.082 mg/kg</td> <td>-0.067 – -0.096</td> </tr> </tbody> </table> <p>The authors indicate that, although the recommended initial dose of warfarin is 0.2 mg/kg/day in children, variant heterozygotes and homozygotes may require only 0.17 and 0.12 mg/kg/day as an initial maintenance dose, respectively. This corresponds to 85% and 60% of the normal dose.</p> <p>Heterogeneity between the studies was low for the comparison of *1/*2+*1/*3 with *1/*1 and absent for the comparison of *2/*2+*2/*3+*3/*3 with *1/*1.</p>	Dose compared to *1/*1:				standardized mean difference	95% CI	*1/*2+*1/*3	-0.512	-0.311 – -0.713	This indicates a moderate effect on the dose.			*2/*2+*2/*3+*3/*3	-1.099	-0.670 – -1.528	This indicates a large effect on the dose.			Daily dose compared to *1/*1:				mean difference	95% CI	*1/*2+*1/*3	-0.033 mg/kg	-0.019 – -0.047	*2/*2+*2/*3+*3/*3	-0.082 mg/kg	-0.067 – -0.096	
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<p>ref. 6 Wang F et al. Efficacy and safety of genotype-guided warfarin dosing in the Chinese population: a meta-analysis of randomized control-</p>	<p>3</p>	<p>Meta-analysis of 14 randomized controlled trials with 2137 Chinese patients comparing genotype-guided dosing with not genotype-guided dosing. For bleeding, the meta-analysis included 7 trials with a total of 671 and 695 patients in the genotype-guided and not-genotype guided groups, respectively. For adverse events, the meta-analysis included 6 trials with a total of 466 and 458 patients in the genotype-guided and not-genotype guided groups, respectively.</p>	<p>Author’s conclusion: ‘Genotype-guided warfarin-dosing algorithms could improve the efficacy and safety of warfarin anticoa-</p>																														

<p>led trials. J Cardiovasc Pharmacol 2019;73:127-35. PMID: 30688796.</p> <p>ref. 6, continuation</p>	<p>geno-</p>	<p>For percentage of patients who received a warfarin-stable therapeutic dose during follow-up, the meta-analysis included 5 trials with a total of 289 and 284 patients in the genotype-guided and not-genotype guided groups, respectively. For time to first therapeutic INR, the meta-analysis included 5 trials with a total of 473 and 487 patients in the genotype-guided and not-genotype guided groups, respectively. For time to stable therapeutic dose, the meta-analysis included 6 trials with a total of 372 and 372 patients in the genotype-guided and not-genotype guided groups, respectively. For INR > 4, the meta-analysis included 4 trials with a total of 677 patients. The follow-up duration varied from 30 to 180 days. In 7 trials, initial dose in the not-genotype-guided group was fixed. In the other 7 trials, two or three fixed initial doses were used based on weight or not specified criteria (n = 3) or the initial dose was based on clinical parameters (n = 4). Genotype-guided dosing was based on the genotypes of VKORC1 and CYP2C9 in all trials. The therapeutic INR range differed from 2-3 or 1.8-3 in 2 of the 14 trials.</p> <p>Quality of the included trials was assessed with the Cochrane Risk Assessment Tool. The risk of bias in six domains was assessed: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other bias. In the table in the study low risk seems to be indicated with high (quality). Of the 14 included trials, 4 had a low risk of bias in 3 domains, an unclear risk in 2 domains (allocation concealment and blinding in 3 studies, and allocation concealment and other bias in 1 study) and a high risk in 1 domain (other bias in 3 studies, and blinding in 1 study), 1 had a low risk in 3 domains, an unclear risk in 1 domain (allocation concealment) and a high risk in 2 domains (blinding and other bias), 1 had a low risk in 1 domain, an unclear risk in 2 domains (allocation concealment and other bias) and a high risk in 3 domains (blinding, incomplete outcome data, and selective reporting), 1 had an unclear risk in 4 domains (random sequence generation, allocation concealment, blinding, and other bias) and a high risk in 2 domains (incomplete outcome data and selective reporting), and 7 had an unclear risk in 3 domains (allocation concealment, blinding and other bias) and a high risk in 3 domains (random sequence generation, incomplete outcome data, and selective reporting). The authors indicate that the 5 studies with low risk of bias in 3 domains were categorised as high quality.</p> <p>The outcome adverse events included excessive INR, bleeding, or thrombosis. A stable warfarin therapeutic dose was defined as at least 7 days where the patient's INR values remained within the therapeutic range.</p> <p>Meta-analyses were performed with a random-effects model in case of substantial heterogeneity between the studies and with a fixed-effect model in case of low or absent heterogeneity. This indicates that the statistical method was chosen afterwards. The search and selection strategy was transparent, but the data extraction was not described.</p> <p>Publication bias analysis was performed with funnel plots only and data were not shown.</p> <p>4 of the trials in this meta-analysis were also included in the network meta-analysis of Sridharan 2021.</p> <p>Results:</p> <table border="1" data-bbox="531 2002 1233 2094"> <tr> <td colspan="2">Genotype-guided in comparison with not-genotype-guided therapy:</td> </tr> <tr> <td></td> <td>inci-</td> </tr> </table>	Genotype-guided in comparison with not-genotype-guided therapy:			inci-	<p>gulation in the Chinese population.'</p>
Genotype-guided in comparison with not-genotype-guided therapy:							
	inci-						

ref. 6, continuation	type-guided versus not genotype-guided therapy: AA#			dence in the not-genotype guided group		
		bleeding events	OR = 0,24 (95% CI: 0,11-0,52) (S)	5%		
		adverse events	OR = 0,60 (95% CI: 0,43-0,83) (S)	25%		
		% of patients who received a warfarin-stable therapeutic dose during follow-up	OR = 2,68 (95% CI: 1,82-3,95) (S)	63%		
		time to first therapeutic INR	mean difference = -1,87 days (95% CI: -0,32 - -3,41) (S)			
		time to stable therapeutic dose	mean difference = -7,98 days (95% CI: -6,87 - -9,08) (S)			
		INR > 4	NS			
		The heterogeneity between the studies was high or substantial for the meta-analyses investigating time to first therapeutic INR, time to stable therapeutic dose, and INR > 4. Heterogeneity between the studies was absent or low for the other meta-analyses.				
		Sensitivity analysis was performed by deselecting the studies one by one. This did not change the overall results for bleeding events, adverse events, percentage of patients who received a warfarin-stable therapeutic dose during follow-up, and INR > 4. For time to stable therapeutic dose, subgroup analysis showed no obvious differences in outcome results, but heterogeneity between the studies disappeared after exclusion of the 2 studies, where dose adjustment in the not-genotype-guided group was performed according to a usual local clinical procedure. In the remaining 4 studies, initial doses were fixed in the not-genotype-guided group. For time to first therapeutic INR, the meta-analysis result changed after removal of the largest study (Liu 2014 with 203 and 212 patients in the genotype-guided and not-genotype guided group, respectively (mean difference = -2,57 (95% CI: -1,86 - -3,28) (S)), while in addition, heterogeneity between the studies was reduced by the removal. The time to first therapeutic INR in the study of Liu 2014 was lower than that in the other 4 studies in the meta-analysis, possibly because the therapeutic INR ranges in this study were lower (1,6-2,2 and 1,8-2,5) and because the study included patients who had used warfarin in the past three months.				
		There were no indications for publication bias.				
ref. 7 Tse G et al. Genotype-guided warfarin dosing vs. conventional dosing strategies: a systematic review and meta-analysis of randomized controlled trials.	4	Meta-analysis of 18 randomized controlled trials with 5230 patients comparing genotype-guided dosing (n = 2626) with not genotype-guided dosing (n = 2604). The number of studies included in the meta-analyses are 3 for time to first therapeutic INR, 5 for time to first stable INR, 13 for time in therapeutic range, 13 for INR ≥ 4, 13 for bleeding, 7 for thromboembolism, and 6 for mortality. The number of patients per trial varied from 38 to 1607. The follow-up duration varied from 21 to 90 days. In 11 trials, initial dose in the not-genotype-guided group was fixed. In the other 7		Author's conclusion: 'Genotype-guided warfarin dosing offers better safety with less bleeding compared with conventional dosing strategies. No significant		

Br J Clin Pharmacol
2018;84:1868-82.
PMID: 29704269.

ref. 7, continuation

trials, it was calculated with a clinical algorithm. In all trials, genotype-guided dose was calculated with an algorithm including clinical parameters. Genotype-guided dosing was based on the genotypes of VKORC1 and CYP2C9 in 13 trials, on the genotypes of VKORC1, CYP2C9, and CYP-4F2 in 3 trials, and on the genotype of CYP2C9 in 2 trials. The therapeutic INR range differed between the trials. Quality of the included trials was assessed with the Cochrane Risk Assessment Tool. The risk of bias in seven domains was assessed: random sequence generation and allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias. Of the 18 included trials, 1 had a low risk of bias in all 7 domains, 6 had an uncertain risk in 1 domain (blinding of outcome assessment), 1 had an uncertain risk in 2 domains (allocation concealment and blinding of participants and personnel), 3 had an uncertain risk in 3 domains (random sequence generation, allocation concealment, and blinding of outcome assessment), 2 had an uncertain risk in 4 domains (random sequence generation, allocation concealment, blinding of participants and personnel, and blinding of outcome assessment), 2 had an uncertain risk in all 7 domains (conference abstracts), 1 had a high risk in 1 domain (blinding of participants and personnel), 1 had a high risk in 1 domain (other bias) and an uncertain risk in 3 domains (random sequence generation, allocation concealment, and blinding of outcome assessment), and 1 had a high risk in 2 domains (random sequence generation and selective reporting) and an uncertain risk in 3 domains (allocation concealment, blinding of participants and personnel, and blinding of outcome assessment). Meta-analyses were performed with a random-effects model in case of substantial heterogeneity between the studies and with a fixed-effect model in case of low or absent heterogeneity. This indicates that the statistical method was chosen afterwards. The search and selection strategy was transparent and the data extraction was standardised. Publication bias analysis was performed with funnel plot and Egger's test, but only for the meta-analyses with all trials, not for the stratifications. All 18 trials in this meta-analysis were also included in the network meta-analysis of Sridharan 2021 and 3 of the trials in the meta-analysis of Wang 2010.

benefit on thromboembolism or mortality was evident.'

Results:

Genotype-guided in comparison with not-genotype-guided therapy:		
time to first therapeutic INR (mean difference ± standard error)	all (3 trials, all fixed initial dose control)	-2.60 ± 0.26 days (S)
	Whites (2 trials)	-2.72 ± 0.35 days (S)
	Chinese (1 trial)	-2.46 ± 0.39 days (S)
time to stable INR (mean difference ± standard error)	all (5 trials)	-5.9 ± 2.0 days (S)
	fixed initial dose control (4 trials)	-6.42 ± 0.31 days (S) (fixed-effects model used despite significant heterogeneity, so overestimation of the effect)
	clinical information control (1 trial)	NS

ref. 7, continuation					
genotype-guided versus not genotype-guided therapy: AA [#]		Whites (2 trials)	NS		
		Whites and Africans (1 trial)	NS		
		Chinese (2 trials)	-5.1 ± 1.9 days (S)		
	% of time within the therapeutic INR range (mean difference ± standard error)	all (13 trials)	+3.1 ± 1.2% (S)		
		fixed initial dose control (9 trials)	+7.4 ± 2.0% (S)		
		clinical information control (4 trials)	NS		
		Whites (7 trials)	+4.9 ± 3.0% (S)		
		Whites and Africans (3 trial)	NS		
		Chinese (3 trials)	+9.2 ± 1.7% (S)		
	INR ≥ 4	all (13 trials)	RR = 0.87 (95% CI: 0.78-0.98) (S)		
		fixed initial dose control (8 trials)	RR = 0.82 (95% CI: 0.68-0.99) (S)		
		clinical information control (5 trials)	NS		
		Whites (6 trials)	NS		
		Whites and Africans (3 trial)	NS		
		Chinese (4 trials)	NS		
		bleeding	all (13 trials)	RR = 0.82 (95% CI: 0.69-0.98) (S)	Based on the absolute risk difference, the calculated number needed to genotype to prevent one event of major bleeding was 40.
	fixed initial dose control (8 trials)		NS		
	clinical information control (7 trials)		NS		
	Whites (5 trials)		NS		
	Whites and Africans (4 trials)		NS		
	Chinese (4 trials)		RR = 0.46 (95% CI: 0.23-0.92) (S)		
	thromboembolism		all (7 trials)	NS	
			fixed initial dose control (2 trials)	NS	
			clinical information control (5 trials)	NS	
		Whites (3 trials)	NS		
		Whites and Africans (3 trials)	NS		
		Chinese (1 trial)	NS		
	mortality	all (6 trials)	NS		
		fixed initial dose control (2 trials)	NS		
		clinical information control (4 trials)	NS		
		Whites (3 trials)	NS		

ref. 7, continuation		<table border="1"> <tr> <td data-bbox="730 73 962 136">Whites and Africans (2 trials)</td> <td data-bbox="962 73 1243 136">NS</td> </tr> <tr> <td data-bbox="730 136 962 170">Chinese (1 trial)</td> <td data-bbox="962 136 1243 170">NS</td> </tr> </table> <p data-bbox="531 170 1243 264">Heterogeneity between the trials was significant for: - time to stable INR - percentage of time within the therapeutic INR range</p> <p data-bbox="531 264 1243 360">Indications for publication bias were found for the meta-analysis investigating bleeding risk, but not for the other meta-analyses.</p>	Whites and Africans (2 trials)	NS	Chinese (1 trial)	NS									
Whites and Africans (2 trials)	NS														
Chinese (1 trial)	NS														
<p data-bbox="113 360 387 790">ref. 8 Zhang J et al. Impact of CYP2C9, VKORC1 and CYP4F2 genetic polymorphisms on maintenance warfarin dosage in Han-Chinese patients: A systematic review and meta-analysis. Meta Gene 2016;9:197-209. PMID: 27617219.</p>	<p data-bbox="387 360 523 394">3</p> <p data-bbox="387 1200 523 1263">*1/*3: A *3/*3: A</p>	<p data-bbox="523 360 1243 1066">Meta-analysis of 19 studies with Han-Chinese patients. The meta-analysis comparing *1/*3 with *1/*1 contained 19 studies with a total of 338 *1/*3 and 3534 *1/*1. The meta-analysis comparing *3/*3 with *1/*1 contained 4 studies with a total of 8 *3/*3 and 819 *1/*1. 3 studies containing only 1 *3/*3 were excluded from the meta-analysis comparing *3/*3 and *1/*1. Studies differed in the target INR. Quality of the included studies was analysed with the checklist recommended by the Cochrane handbook as well as other methods recommended in related literature, but results are not shown. Meta-analyses were performed with a random-effects model in case of significant or moderate or high heterogeneity between the studies and with a fixed-effect model in case of insignificant or low heterogeneity. This indicates that the statistical method was chosen afterwards. The search and selection strategy was transparent and the data extraction was standardised. Publication bias analysis was performed with funnel plots, but results are not shown. 7 of the 19 studies in this meta-analysis were included in the meta-analysis of Zhang 2024.</p> <p data-bbox="523 1099 628 1126">Results:</p> <table border="1" data-bbox="531 1126 1235 1263"> <thead> <tr> <th colspan="3" data-bbox="531 1126 1235 1160">Dose compared to *1/*1:</th> </tr> <tr> <th data-bbox="531 1160 715 1193"></th> <th data-bbox="715 1160 1002 1193">mean difference (%)</th> <th data-bbox="1002 1160 1235 1193">95% CI</th> </tr> </thead> <tbody> <tr> <td data-bbox="531 1193 715 1227">*1/*3</td> <td data-bbox="715 1193 1002 1227">-28%</td> <td data-bbox="1002 1193 1235 1227">-22 – -33</td> </tr> <tr> <td data-bbox="531 1227 715 1263">*3/*3</td> <td data-bbox="715 1227 1002 1263">-72%</td> <td data-bbox="1002 1227 1235 1263">-62 – -81</td> </tr> </tbody> </table> <p data-bbox="531 1263 1243 1547">Heterogeneity between the studies was high for the comparison of *1/*3 and *1/*1. Heterogeneity between the studies was absent for the comparison of *3/*3 and *1/*1. Meta-regression analysis showed that neither year of publication, language of the publication (English or Chinese), study location, age, number of patients, male ratio and median INR explained the observed heterogeneity for the comparison of *1/*3 and *1/*1.</p> <p data-bbox="531 1547 1243 1742">Sensitivity analysis was performed by deselecting the studies one by one in chronological order. The results were not changed greatly when any study was deselected, and no study was found to be significantly associated with statistical heterogeneity, which indicated that the results of the analysis were stable and reliable.</p> <p data-bbox="531 1742 1243 1776">There were no indications for publication bias.</p>	Dose compared to *1/*1:				mean difference (%)	95% CI	*1/*3	-28%	-22 – -33	*3/*3	-72%	-62 – -81	<p data-bbox="1243 360 1492 763">Author's conclusion: 'The results showed that SNPs of CYP2C9, CYP4F2, VKORC1 1173 and VKORC1-1639 significantly influenced the mean daily warfarin dosage in Han-Chinese patients.'</p>
Dose compared to *1/*1:															
	mean difference (%)	95% CI													
*1/*3	-28%	-22 – -33													
*3/*3	-72%	-62 – -81													
<p data-bbox="113 1776 387 2112">ref. 9 Liao Z et al. Meta-analysis of randomized controlled trials reveals an improved clinical outcome of using genotype plus clinical algorithm for warfarin dosing. J Thromb Thrombo-</p>	<p data-bbox="387 1776 523 1809">4</p>	<p data-bbox="523 1776 1243 2112">Meta-analysis of 7 randomized controlled trials with 1,910 patients comparing genotype-guided dosing (n = 960) with not genotype-guided dosing (n = 950). The number of patients per trial varied from 38 to 1,015. The follow-up duration was not reported for one trial and varied from 46 to 180 days for the other six. In 4 trials, initial dose in the not-genotype-guided group was fixed. In the other 3 trials, it was calculated with a clinical algorithm. Except for the smallest trial, genotype-guided dosing was based on the genotypes of both CYP2C9 and VKORC1. The therapeutic INR range differed between the trials.</p>	<p data-bbox="1243 1776 1492 2112">Author's conclusion: 'Allocation to genotype plus clinical algorithm may be associated with a significant improvement of the percentage of time within the therapeutic INR</p>												

<p>lysis 2015;39:228-34. PubMed PMID: 24962733.</p> <p>ref. 9, continuation</p>	<p>geno- type- guided versus not geno- type- guided therapy: AA#</p>	<p>Risk of bias of the included trials was assessed, including masking of outcome assessments (present in 6 of the 7 trials), allocation concealment (present in all 7 trials), intention-to treat analysis (present in all 7 trials), and early trial stopping for efficacy (absent in all 7 trials). Adverse events were defined as major bleeding, thromboembolism, myocardial infarction, death from any cause, any clinical relevant non-major bleeding event or other conditions requiring emergency medical management, INR > 4 (3 trials) or INR > 3,5 (1 trial).</p> <p>A fixed-effects model was used in all analyses, also if there was heterogeneity between the studies. This indicates that the statistical method was chosen prospectively, but that the wrong statistical method was chosen for percentage of time within the therapeutic INR range, all trials. A fixed-effects model overestimates the effect in case of significant heterogeneity. The search and selection strategy was transparent and the data extraction was standardised. Publication bias analysis was performed with funnel plot and Egger's test (with p < 0.10 considered significant). All 7 trials in this meta-analysis were also included in the network meta-analysis of Sridharan 2021 and the meta-analysis of Tse 2018, and 1 trial in the meta-analysis of Wang 2019.</p> <p>Results:</p> <table border="1" data-bbox="531 869 1225 1400"> <thead> <tr> <th colspan="4">Genotype-guided in comparison with not-genotype-guided therapy:</th> </tr> <tr> <th></th> <th></th> <th></th> <th>% of patients in not-genotype-guided group</th> </tr> </thead> <tbody> <tr> <td rowspan="2">% of time within the therapeutic INR range (standardized mean difference)</td> <td>all (5 trials, n = 1,729)</td> <td>NS</td> <td></td> </tr> <tr> <td>fixed initial dose (3 trials, n < 700)</td> <td>+0.24 (95% CI: 0.09-0.40) (S)</td> <td></td> </tr> <tr> <td>Adverse events</td> <td>4 trials, n = 1,763</td> <td>NS</td> <td>38%</td> </tr> <tr> <td>Death</td> <td>3 trials, n = 1,571</td> <td>NS</td> <td>0.64%</td> </tr> </tbody> </table> <p>Heterogeneity between the trials was only significant and moderate for: - percentage of time within the therapeutic INR range, all trials</p> <p>Indications for publication bias were not found.</p>	Genotype-guided in comparison with not-genotype-guided therapy:							% of patients in not-genotype-guided group	% of time within the therapeutic INR range (standardized mean difference)	all (5 trials, n = 1,729)	NS		fixed initial dose (3 trials, n < 700)	+0.24 (95% CI: 0.09-0.40) (S)		Adverse events	4 trials, n = 1,763	NS	38%	Death	3 trials, n = 1,571	NS	0.64%	<p>range for patients adopting fixed dose of warfarin. The incidence of total adverse events and death rates did not differ between these two groups.'</p>
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<p>ref. 10 Xu H et al. Meta-analysis of efficacy and safety of genotype-guided pharmacogenetic dosing of warfarin. Int J Cardiol 2014;177:654-7. PubMed PMID: 25449474.</p>	<p>4</p>	<p>Meta-analysis of 8 randomized controlled trials with 2,158 patients comparing genotype-guided dosing (n = 1,084) with not genotype-guided dosing (n = 1,074). The number of patients per trial varied from 26 to 955. The follow-up duration varied from 28 to 90 days. In 5 trials, initial dose in the not-genotype-guided group was fixed. In the other 3 trials, it was calculated with a clinical algorithm. In 6 trials, genotype-guided dosing was based on the genotypes of CYP2C9 and VKORC1. In 1 trial it was based only on the CYP2C9 genotype and in 1 trial on the genotypes of CYP2C9, VKORC1 and CYP4F2.</p> <p>The therapeutic INR range differed between the trials. Quality of the included trials was assessed with the Jadad scale. Of the included trials, 4 scored the maximum of 7 points on this scale, 2 scored 6 points, 1 scored 4 points and 1 scored 3 points.</p> <p>Meta-analyses were performed with a random-effects model in case of significant heterogeneity between the</p>	<p>Author's conclusion: 'We found that time in the therapeutic INR range of the genotype-guided group was increased compared with the control group in the RCTs when the initial warfarin dose was fixed. However, the genotype-guided group failed to exhibit statistically significant outcome compared</p>																							

<p>ref. 10, continuation</p>	<p>geno- type- guided versus not geno- type- guided therapy: AA#</p>	<p>studies and with a fixed-effect model in the absence of heterogeneity. This indicates that the statistical method was chosen afterwards. The search and selection strategy was transparent and the data extraction was standardised. Publication bias analysis was performed with Begg and Egger's test.</p> <p>All 8 trials in this meta-analysis were also included in the meta-analysis of Tse 2018, 5 in the meta-analysis of Liao 2015, and 1 in the meta-analysis of Wang 2019.</p> <p>Results:</p> <table border="1" data-bbox="531 414 1233 1641"> <thead> <tr> <th colspan="4">Genotype-guided in comparison with not-genotype-guided therapy:</th> </tr> <tr> <th></th> <th></th> <th></th> <th>% in not-genotype-guided group</th> </tr> </thead> <tbody> <tr> <td rowspan="5">% of time within the therapeutic INR range (standardized mean difference)</td> <td>all (8 trials)</td> <td>Not determined due to high heterogeneity</td> <td></td> </tr> <tr> <td>fixed initial dose (5 trials, n = 812)</td> <td>+0.30 (95% CI: 0.08-0.53) (S)</td> <td></td> </tr> <tr> <td>not fixed initial dose (3 trials, n = 1,286)</td> <td>NS</td> <td></td> </tr> <tr> <td>follow-up ≤ 28 days (3 trials, n = 1,218)</td> <td>NS</td> <td></td> </tr> <tr> <td>follow-up > 28 days (5 trials, n = 880)</td> <td>+0.25 (95% CI: -0.00-0.51) (NS, trend)</td> <td></td> </tr> <tr> <td>Major bleeding</td> <td>8 trials</td> <td>NS</td> <td>2.6%</td> </tr> <tr> <td>Minor bleeding</td> <td></td> <td>NS</td> <td></td> </tr> <tr> <td>Thromboembolic events</td> <td></td> <td>NS</td> <td></td> </tr> <tr> <td>INR > 4</td> <td></td> <td>NS</td> <td></td> </tr> <tr> <td colspan="4">Heterogeneity between the trials was only significant for: - percentage of time within the therapeutic INR range, all trials - percentage of time within the therapeutic INR range, follow-up > 28 days</td> </tr> <tr> <td colspan="4">Indications for publication bias were not found.</td> </tr> </tbody> </table>	Genotype-guided in comparison with not-genotype-guided therapy:							% in not-genotype-guided group	% of time within the therapeutic INR range (standardized mean difference)	all (8 trials)	Not determined due to high heterogeneity		fixed initial dose (5 trials, n = 812)	+0.30 (95% CI: 0.08-0.53) (S)		not fixed initial dose (3 trials, n = 1,286)	NS		follow-up ≤ 28 days (3 trials, n = 1,218)	NS		follow-up > 28 days (5 trials, n = 880)	+0.25 (95% CI: -0.00-0.51) (NS, trend)		Major bleeding	8 trials	NS	2.6%	Minor bleeding		NS		Thromboembolic events		NS		INR > 4		NS		Heterogeneity between the trials was only significant for: - percentage of time within the therapeutic INR range, all trials - percentage of time within the therapeutic INR range, follow-up > 28 days				Indications for publication bias were not found.				<p>to the control group in the studies using equation initial dose. Only a limited recommendation can be made that genotype-guided pharmacogenetic algorithm should be applied to guide warfarin dose rather than fixed dose.</p> <p>The results from our meta-analysis indicated that there was no benefit of genotype-guided dosing of warfarin with respect to hemorrhagic events. But this should be interpreted with caution because of the number of events was relatively small.'</p>
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<p>ref. 11 Franchini M et al. Effects on bleeding complications of pharmacogenetic testing for initial dosing of vitamin K antagonists: a systematic review and meta-analysis. J Thromb Haemost 2014;12:1480-7. PubMed PMID: 25040440.</p>	<p>3</p>	<p>Meta-analysis of 9 randomized controlled trials with 2,812 patients comparing genotype-guided dosing (n = 1,411) with not genotype-guided dosing (n = 1,401). The number of patients per trial varied from 26 to 1015. The mean follow-up period varied from 22 to 90 days. When the information was available, clinical endpoints were referred to a 30-day follow-up period. In 7 trials, genotype-guided dosing was based on the genotypes of CYP2C9 and VKORC1. In 2 trials it was based only on the CYP2C9 genotype. One of the included trials (Verhoef 2013; n = 548) studied acenoumarol and phenprocoumon instead of warfarin. The largest trial (Kimmel 2013) included a significant number of African American patients.</p> <p>Quality of the included trials was assessed according to the Cochrane methodology. The risk of bias in six domains</p>	<p>Author's conclusion: 'The results of this meta-analysis show that genotype-guided initial VKA dosing is able to reduce serious bleeding events by approximately 50% compared with clinically-guided dosing approaches.'</p>																																																

ref. 11, continuation

was assessed: random sequence generation and allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessors (detection bias), incomplete outcome data (attrition bias) and selective outcome reporting (reporting bias). Of the 9 included trials, 1 had a low risk of bias in all 8 subdomains, 1 had an uncertain risk in 1 subdomain (allocation concealment), 1 had an uncertain risk in 2 subdomains (allocation concealment and blinding of participants and personnel), 2 had a high risk in 1 subdomain (blinding of outcome assessment, outcomes mostly or partially based on judgment), 2 had a high risk in 1 subdomain (blinding of outcome assessment, outcomes mostly or partially based on judgment) and an uncertain risk in 1 subdomain (blinding of outcome assessment, outcomes not based on judgment), 1 had a high risk in 1 subdomain (blinding of outcome assessment, outcomes mostly or partially based on judgment) and an uncertain risk in 3 subdomains (random sequence generation, allocation concealment, and blinding of participants and personnel), and 1 had a high risk in 4 subdomains (allocation concealment, blinding of participants and personnel, blinding of outcome assessment, outcomes mostly or partially based on judgment, and selective reporting) and an uncertain risk in 1 subdomain (random sequence generation).

Meta-analyses were performed with a random-effects model in case of heterogeneity between the studies and with a fixed-effect model in the absence of heterogeneity. This indicates that the statistical method was chosen afterwards. The search and selection strategy was transparent and the data extraction was standardised. Possible publication bias was not analysed.

All 9 trials in this meta-analysis were included in the network meta-analysis of Sridharan 2021, 8 in the meta-analysis of Tse 2018, 7 in the meta-analysis of Xu 2014, 6 in the meta-analysis of Liao 2015, and none in the meta-analysis of Wang 2019.

genotype-guided versus not genotype-guided therapy: AA#

Results:

Genotype-guided in comparison with not-genotype-guided therapy:			
			% in not-genotype-guided group
Major bleeding	6 trials, n = 2,131	RR = 0.47 (95% CI: 0.23-0.96) (S)	2.2%
2 trials with 0 major bleeds were excluded from the analysis (n = 481)			
Thromboembolic events		NS	
Deaths		NS	
INR > 4		NS	
% of time within the therapeutic INR range	weighted mean difference	NS	46.8%
	standardized mean difference	NS	
Heterogeneity was very high for the percentage of time within the therapeutic INR range. There was no heterogeneity for the other outcomes.			

ref. 11, continuation		There were not enough data to perform meta-analysis for the following outcomes: time to first therapeutic INR, time to stable warfarin dose, number of patients with INR < 2 and number of days in hospital.																													
<p>ref. 12 Stergiopoulos K et al. Genotype-guided vs clinical dosing of warfarin and its analogues: meta-analysis of randomized clinical trials. JAMA Intern Med 2014;174:1330-8. PubMed PMID: 24935087.</p>	4	<p>Meta-analysis of 9 randomized controlled trials with 2,812 patients comparing genotype-guided dosing (n = 1,411) with not genotype-guided dosing (n = 1,401). The number of patients per trial varied from 26 to 1015. Patients were from the United States, Europe or Israel. The follow-up period varied from 4 weeks to 6 months (median 12 weeks). In 6 trials, genotype-guided dosing was based on the genotypes of CYP2C9 and VKORC1. In 2 trials it was based only on the CYP2C9 genotype and in 1 trial on the genotypes of CYP2C9, VKORC1 and CYP4F2. One of the included trials (Verhoef 2013; n = 548) studied acenoumarol and phenprocoumon instead of warfarin. The therapeutic INR range differed between the trials. Quality of the included trials was assessed by the Jadad scale, with a score of 3 or greater of the maximum score of 5 indicative of high quality. The 5 domains in the Jadad scale were: randomised, double blind, and adequate description of randomisation method, blinding method, and patient attrition and reasons. Of the 9 included trials, 1 scored the maximum of 5 points, 6 scored 3 points (being not double blind and so lacking a description of the blinding method), and 2 scored 2 points (being not double blind and so lacking a description of the blinding method, and in addition lacking an adequate description of the randomisation method). The methods section indicates that quality was also assessed according to the Cochrane methodology with risk of bias in the method of randomization; allocation concealment; patient, investigator, and outcome assessor blinding; selective outcome reporting; incomplete outcome ascertainment; and other potential sources of bias being assessed. However, no data were reported on the Cochrane assessment.</p> <p>Meta-analyses were performed with a random-effects model, so the statistical method was prospectively chosen. However, there was no prospective registration of the study protocol. The search and selection strategy was transparent and the data extraction was standardised. Publication bias was assessed by funnel plots. The 9 trials in this meta-analysis are the same as those in Franchini 2014.</p> <p>Results:</p> <table border="1" data-bbox="531 1485 1225 2078"> <thead> <tr> <th colspan="4" data-bbox="531 1485 1225 1547">Genotype-guided in comparison with not-genotype-guided therapy:</th> </tr> <tr> <th data-bbox="531 1547 826 1700"></th> <th data-bbox="826 1547 999 1700"></th> <th data-bbox="999 1547 1091 1700"></th> <th data-bbox="1091 1547 1225 1700">% in not-genotype-guided group</th> </tr> </thead> <tbody> <tr> <td data-bbox="531 1700 826 1823">% of time within the therapeutic INR range (standardized mean difference)</td> <td data-bbox="826 1700 999 1823">9 trials</td> <td data-bbox="999 1700 1091 1823">NS</td> <td data-bbox="1091 1700 1225 1823"></td> </tr> <tr> <td data-bbox="531 1823 826 1886">INR > 4</td> <td data-bbox="826 1823 999 1886">8 trials, n = 2,621</td> <td data-bbox="999 1823 1091 1886">NS</td> <td data-bbox="1091 1823 1225 1886">28%</td> </tr> <tr> <td data-bbox="531 1886 826 1948">Major bleeding</td> <td data-bbox="826 1886 999 1948">7 trials, n = 2,586</td> <td data-bbox="999 1886 1091 1948">NS</td> <td data-bbox="1091 1886 1225 1948">1.6%</td> </tr> <tr> <td data-bbox="531 1948 826 2011">Thromboembolic events</td> <td data-bbox="826 1948 999 2011">7 trials, n = 2,586</td> <td data-bbox="999 1948 1091 2011">NS</td> <td data-bbox="1091 1948 1225 2011">1.2%</td> </tr> <tr> <td colspan="4" data-bbox="531 2011 1225 2078">Analyses of subgroups based on study quality, study location or sample size did not result in significantly</td> </tr> </tbody> </table>	Genotype-guided in comparison with not-genotype-guided therapy:							% in not-genotype-guided group	% of time within the therapeutic INR range (standardized mean difference)	9 trials	NS		INR > 4	8 trials, n = 2,621	NS	28%	Major bleeding	7 trials, n = 2,586	NS	1.6%	Thromboembolic events	7 trials, n = 2,586	NS	1.2%	Analyses of subgroups based on study quality, study location or sample size did not result in significantly				<p>Author's conclusion: 'In this meta-analysis of randomized clinical trials, a genotype-guided dosing strategy did not result in a greater percentage of time that the INR was within the therapeutic range, fewer patients with an INR greater than 4, or a reduction in major bleeding or thromboembolic events compared with clinical dosing algorithms.'</p>
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ref. 12, continuation		<p>different outcomes. Neither did exclusion of any single trial from the analyses.</p> <p>Heterogeneity was high for the percentage of time with-in the therapeutic INR range. There was no heterogeneity for the other outcomes.</p> <p>Indications for publication bias were not found.</p>																																																																								
<p>ref. 13 Yang J et al. Influence of CYP2C9 and VKORC1 genotypes on the risk of hemorrhagic complications in warfarin-treated patients: a systematic review and meta-analysis. Int J Cardiol 2013;168:4234-43. PubMed PMID: 23932037.</p>	<p>4</p> <p>*1/*3: D</p> <p>*3/*3: C</p>	<p>Meta-analysis of 22 studies with 6272 patients. Patients were Whites in 15 studies, Whites or African-Americans in 3 studies, Asians in 3 studies and Brasilians in 1 study. The follow-up periods for bleeding or over-anticoagulation varied from 3 weeks to 6 years. Quality of the included studies was analysed with the Newcastle-Ottawa Scale. Studies with a score of 7 or greater were considered to be of high quality. Of the 22 included studies, 2 scored the maximum of 9 points on the Newcastle-Ottawa Scale, 6 scored 8 points, 10 scored 7 points, and 4 scored 6 points.</p> <p>Meta-analyses were performed with a random-effects model in case of significant or moderate or high heterogeneity between the studies and with a fixed-effect model in the case of insignificant or low heterogeneity. This indicates that the statistical method was chosen afterwards. The search and selection strategy was transparent and the data extraction was standardised.</p> <p>Publication bias was assessed by funnel plot. In addition, the fail-safe number (N_{fs}) for each meta-analysis was calculated by the following equation: $N_{fs} = (\sum Z/1.64)^2 - k$, ($p = 0.05$), where k is the number of articles included in each meta-analysis. If the N_{fs} for a meta-analysis is smaller than the number of observed studies, the meta-analysis result has a significant possibility of publication bias.</p> <p>Of the 13 studies in this meta-analysis investigating bleeding, 5 were included in the meta-analysis of Zhang 2024.</p> <p>Results:</p> <table border="1" data-bbox="531 1155 1222 1413"> <thead> <tr> <th colspan="5">Bleeding in comparison with *1/*1:</th> </tr> <tr> <th rowspan="2">genotype</th> <th colspan="2">Total bleeding</th> <th colspan="2">Major bleeding</th> </tr> <tr> <th>HR</th> <th>95% CI</th> <th>HR</th> <th>95% CI</th> </tr> </thead> <tbody> <tr> <td>*1/*2</td> <td>NS</td> <td></td> <td>trend</td> <td>0.95-5.40</td> </tr> <tr> <td>*1/*3</td> <td>2.05</td> <td>1.36-3.10</td> <td>2.43</td> <td>1.17-5.06</td> </tr> <tr> <td>*2/*2</td> <td>trend</td> <td>0.80-19.66</td> <td>-</td> <td></td> </tr> <tr> <td>*2/*3</td> <td>NS</td> <td></td> <td>-</td> <td></td> </tr> <tr> <td>*3/*3</td> <td>4.87</td> <td>1.38-17.14</td> <td>trend</td> <td>0.95-24.22</td> </tr> </tbody> </table> <p>Number of studies and patients per genotype for both outcomes: *1/*2: 3 studies, n = 49 and 2 studies, n = 45 *1/*3: 6 studies, n = 127 and 4 studies, n = 79 *2/*2: 2 studies, n = 6 and 0 studies *2/*3: 2 studies, n = 7 and 0 studies *3/*3: 4 studies, n = 10 and 2 studies, n = 7</p> <p>The heterogeneity between the studies was high and significant for *1/*2 and total bleeding.</p> <table border="1" data-bbox="531 1722 1222 2096"> <thead> <tr> <th colspan="5">*2-carrier in comparison with *1/*1:</th> </tr> <tr> <th></th> <th></th> <th>HR</th> <th>95% CI</th> <th>Incidence for *1/*1</th> </tr> </thead> <tbody> <tr> <td rowspan="3">INR > 4 (5 studies, n = 1,672)</td> <td></td> <td>1.52</td> <td>1.11-2.09</td> <td rowspan="3">14%</td> </tr> <tr> <td>0-30 days</td> <td>1.64</td> <td>1.11-2.43</td> </tr> <tr> <td>> 30 days</td> <td>NS</td> <td></td> </tr> <tr> <td rowspan="3">Total bleeding (4 studies, n = 561)</td> <td></td> <td>1.80</td> <td>1.09-2.97</td> <td rowspan="3">11%</td> </tr> <tr> <td>Whites</td> <td>trend</td> <td>0.99-2.86</td> </tr> <tr> <td>Asians</td> <td>-</td> <td></td> </tr> </tbody> </table>	Bleeding in comparison with *1/*1:					genotype	Total bleeding		Major bleeding		HR	95% CI	HR	95% CI	*1/*2	NS		trend	0.95-5.40	*1/*3	2.05	1.36-3.10	2.43	1.17-5.06	*2/*2	trend	0.80-19.66	-		*2/*3	NS		-		*3/*3	4.87	1.38-17.14	trend	0.95-24.22	*2-carrier in comparison with *1/*1:							HR	95% CI	Incidence for *1/*1	INR > 4 (5 studies, n = 1,672)		1.52	1.11-2.09	14%	0-30 days	1.64	1.11-2.43	> 30 days	NS		Total bleeding (4 studies, n = 561)		1.80	1.09-2.97	11%	Whites	trend	0.99-2.86	Asians	-		<p>Author's conclusion: 'Both CYP2C9 and VKORC1 genotypes are associated with an increased risk for warfarin over-anticoagulation. CYP2C9*3 is the main genetic risk factor for warfarin haemorrhagic complications.'</p>
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ref. 13, continuation	(*1/*2 + *2/*2 + *2/*3): D	Major bleeding (2 studies, n = 252)	2.56	1.15-5.69	10%	
		<p>There was no significant heterogeneity between the studies.</p> <p>There were no indications for publication bias.</p> <p>Except for total bleeding, the HR's were not influenced by the omission of any individual study from the analyses.</p> <p>For total bleeding, significance was lost after exclusion of either Margaglione 2000, Higashi 2002 or Lima 2008 from the analysis.</p>				
	(*1/*3 + *2/*3 + *3/*3): D	*3-carrier in comparison with *1/*1:				
			HR	95% CI	Incidence for *1/*1	
		INR > 4 (6 studies, n = 1,803)	2.37	1.46-3.83	13%	
		0-30 days	2.48	1.56-3.96		
		> 30 days	1.86	1.08-3.20		
		Total bleeding (8 studies, n = 1,325)	1.95	1.38-2.78	23%	
		Whites	1.90	1.18 -3.05		
		Asians	1.85	1.06-3.20		
		Major bleeding (7 studies, n = 1,572)	2.55	1.29-5.02	6,5%	
The heterogeneity between the studies was moderate but not significant for :						
- INR > 4						
There were no indications for publication bias.						
The HR's were not influenced by the omission of any individual study from the analyses.						
(*2- and/or *3-carrier) in comparison with *1:						
			HR	95% CI	Incidence for *1/*1	
		INR > 4 (11 studies, n = 4,717)	1.90	1.58-2.29	20%	
		0-30 days	1.91	1.58-2.38		
		> 30 days	1.69	1.21-2.36		
		Total bleeding (13 studies, n = 2,670)	1.68	1.34-2.11	22%	
		Whites	1.42	1.05-1.92		
		Asians	1.85	1.06-3.20		
		Major bleeding (7 studies, n = 1,572)	2.19	1.33-3.60	7.7%	
The heterogeneity between the studies was moderate but not significant for :						
- major bleeding						
There were no indications for publication bias.						
The HR's were not influenced by the omission of any individual study from the analyses.						
The incidence of major bleeding in (*2- and/or *3-carriers) was 17,7%.						
The meta-analysis for major bleeding included 3 studies in non-Saudi Whites. The incidence of major bleeding in *1/*1 and (*2- and/or *3-carriers) in these 3 studies was 9.9% and 18.9%, respectively, while 25.9% of the patients in these studies were (*2 and/or *3 carriers)..						
ref. 14	3	Meta-analysis of 34 studies. 31 of the included studies investigated warfarin dose, 13 investigated bleeding, 4 investigated time to stable dose and 2 investigated time to				Author's conclusion:

and VKORC1 on patient response to warfarin: a systematic review and meta-analysis. PLoS One 2012;7:e44064. PubMed PMID: 22952875.

ref. 14, continuation

therapeutic INR. Most studies were retrospective cohorts. The authors use the absence of 0 instead of 1 in the 95% confidence interval of odds ratios to distinguish significance from non-significance. They do not explain this in the article. They might be either looking at a logarithm of the odds ratio or at an odds difference. Methodological quality of the included studies was assessed qualitatively by applying the checklist of Jorgensen and Williams. Description was also qualitative and arranged by quality assessment criterium instead of by study. Meta-analyses were performed with a random-effects model, so the statistical method was chosen prospectively. The review protocol was registered prospectively in the HuGENet database. The search and selection strategy was transparent and the data extraction was standardised. Possible publication bias was not assessed. Of the 31 included studies in this meta-analysis investigating warfarin dose, 3 were included in the meta-analysis of Zhang 2016 and the Black-African patients of 1 study were included in the meta-analysis of Asiimwe 2020. Of the 13 studies in this meta-analysis investigating bleeding, 9 were included in the meta-analysis of Yang 2013 and 3 in the meta-analysis of Zhang 2024.

'Pooled effect estimates were significant in most ethnic groups for CYP2C9*3 and stable dose (mutant types requiring between 1.1 and 2.3 mg/day).'

*1/*2: A

Results:

*1/*2 in comparison with *1/*1:			
			95% CI
Dose (mg/day) (difference in means) (16 studies)		-0.96	-1.73 - -0.19
	Whites	NS	
	Whites/Afro-Americans	-1.90	-3.51 - -0.29
	Indians/Chinese/Malay	NS	
Total bleeding (odds ratio (OR)) (4 studies)	Whites (all 4 studies)	NS	
	The result remained NS after exclusion of the only study that only counted serious or life-threatening bleeds.		
The heterogeneity between studies was significant for: - dose, Whites			

*1/*3: A

*1/*3 in comparison with *1/*1:			
			95% CI
Dose (mg/day) (difference in means) (25 studies)		-1.61	-2.79 - -0.43
	Whites	-1.79	-3.30 - -0.28
	Whites/Afro-Americans	NS	
	Chinese	-1.13	-1.52 - -0.74
	Japanese	-1.18	-1.78 - -0.58
	Indians/Chinese/Malay	-1.47	-2.16 - -0.78
Total bleeding (OR) (8 studies)		NS	
	Whites	NS	

*2/*2: A

*2/*2 in comparison with *1/*1:			
			95% CI
Dose (mg/day) (difference in means) (9 studies)		-1.46	-2.00 - -0.92
	Whites	NS	
	Whites/Afro-Americans	NS	
Total bleeding	Whites (all 4 studies)	NS	

<p>ref. 14, continuation</p>	<p>*3/*3: C</p> <p>(*2/*2 + *2/*3 + *3/*3): A</p>	<table border="1"> <tr> <td>(OR) (4 studies)</td> <td colspan="3">The result remained NS after exclusion of the only study that only counted serious or life-threatening bleeds.</td> </tr> <tr> <td colspan="4">The heterogeneity between studies was significant for: - dose, Whites - total bleeding</td> </tr> <tr> <td colspan="4">*3/*3 in comparison with *1/*1:</td> </tr> <tr> <td colspan="3"></td> <td>95% CI</td> </tr> <tr> <td rowspan="2">Dose (mg/day) (difference in means) (4 studies)</td> <td></td> <td>-1.64</td> <td>-3.31 - -1.97</td> </tr> <tr> <td>Whites</td> <td>-2.29</td> <td>-2.98 - -1.60</td> </tr> <tr> <td rowspan="2">Total bleeding (OR) (5 studies)</td> <td></td> <td>1.18</td> <td>0.04-2.31 (S)</td> </tr> <tr> <td>Whites</td> <td>NS</td> <td></td> </tr> <tr> <td colspan="4">(*1/*2 + *1/*3) in comparison with *1/*1:</td> </tr> <tr> <td colspan="3"></td> <td>95% CI</td> </tr> <tr> <td rowspan="3">Dose (mg/day) (difference in means) (6 studies)</td> <td></td> <td>-1.31</td> <td>-2.20 - -0.42</td> </tr> <tr> <td>Whites</td> <td>-1.55</td> <td>-2.38 - -0.72</td> </tr> <tr> <td>Israeli-Jewish</td> <td>-1.20</td> <td>-1.41 - -0.99</td> </tr> <tr> <td>Total bleeding (OR) (2 studies)</td> <td>Whites (both studies)</td> <td>NS</td> <td></td> </tr> <tr> <td colspan="4">(*2/*2 + *2/*3 + *3/*3) in comparison with *1/*1:</td> </tr> <tr> <td colspan="3"></td> <td>95% CI</td> </tr> <tr> <td rowspan="3">Dose (difference in means) (6 studies)</td> <td></td> <td>-3.56</td> <td>-4.29 - -2.84</td> </tr> <tr> <td>Whites</td> <td>-3.35</td> <td>-4.29 - -2.41</td> </tr> <tr> <td>Israeli-Jewish</td> <td>-3.60</td> <td>-3.99 - -3.21</td> </tr> <tr> <td colspan="4">(*2- and/or *3-carrier) in comparison with *1/*1:</td> </tr> <tr> <td colspan="3"></td> <td>95% CI</td> </tr> <tr> <td rowspan="2">Longer time to stable dose (HR) (4 studies)</td> <td>Whites</td> <td>NS</td> <td></td> </tr> <tr> <td>Afro-Americans</td> <td>NS</td> <td></td> </tr> <tr> <td>Longer time to therapeutic INR (2 studies)</td> <td>Whites (both studies)</td> <td>NS</td> <td></td> </tr> <tr> <td colspan="4">There were not enough data for a meta-analysis of the influence of genotype on INR > 4 during the first week and on time in the therapeutic INR range.</td> </tr> </table>	(OR) (4 studies)	The result remained NS after exclusion of the only study that only counted serious or life-threatening bleeds.			The heterogeneity between studies was significant for: - dose, Whites - total bleeding				*3/*3 in comparison with *1/*1:							95% CI	Dose (mg/day) (difference in means) (4 studies)		-1.64	-3.31 - -1.97	Whites	-2.29	-2.98 - -1.60	Total bleeding (OR) (5 studies)		1.18	0.04-2.31 (S)	Whites	NS		(*1/*2 + *1/*3) in comparison with *1/*1:							95% CI	Dose (mg/day) (difference in means) (6 studies)		-1.31	-2.20 - -0.42	Whites	-1.55	-2.38 - -0.72	Israeli-Jewish	-1.20	-1.41 - -0.99	Total bleeding (OR) (2 studies)	Whites (both studies)	NS		(*2/*2 + *2/*3 + *3/*3) in comparison with *1/*1:							95% CI	Dose (difference in means) (6 studies)		-3.56	-4.29 - -2.84	Whites	-3.35	-4.29 - -2.41	Israeli-Jewish	-3.60	-3.99 - -3.21	(*2- and/or *3-carrier) in comparison with *1/*1:							95% CI	Longer time to stable dose (HR) (4 studies)	Whites	NS		Afro-Americans	NS		Longer time to therapeutic INR (2 studies)	Whites (both studies)	NS		There were not enough data for a meta-analysis of the influence of genotype on INR > 4 during the first week and on time in the therapeutic INR range.				<p>Author's conclusion: 'Compared to the CYP2C9*1/*1 genotype, the CYP2C9*1/*2, CYP2C9*1/*3, CYP2C9*2/*2, CYP2C9*2/*3, and CYP2C9*3/*3 required warfarin doses that were 19.6, 33.7, 36.0, 56.7, and 78.1%</p>
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<p>ref. 15 Lindh JD et al. Influence of CYP2C9 genotype on warfarin dose requirements--a systematic review and meta-analysis. Eur J Clin Pharmacol 2009;65:365-75. PubMed PMID: 19031075.</p>	<p>3</p>	<p>Meta-analysis of 39 studies with 7,907 patients (5,749 *1/*1, 1,216 *1/*2, 759 *1/*3, 78 *2/*2, 81 *2/*3, and 24 *3/*3). 14 studies were performed in Europe, 13 in America and 12 in Asia. Studies were clinical cohorts or cross-sectional studies. Studies differed in target INR and in whether interacting drugs were excluded or not. In the meta-analyses, alleles other than *2 and *3 were considered wild type (*1). Quality of the included studies was not analysed. Meta-analyses were performed with a random-effects model in case of substantial heterogeneity between the studies and with a fixed-effect model in the absence of substantial heterogeneity. This indicates that the statistical method was chosen afterwards. The search and selection strategy was transparent and the data extraction was stan-</p>	<p>Author's conclusion: 'Compared to the CYP2C9*1/*1 genotype, the CYP2C9*1/*2, CYP2C9*1/*3, CYP2C9*2/*2, CYP2C9*2/*3, and CYP2C9*3/*3 required warfarin doses that were 19.6, 33.7, 36.0, 56.7, and 78.1%</p>																																																																																													

<p>ref. 15, continuation</p>	<p>*1/*2: A</p> <p>*1/*3: A</p> <p>*2/*2: A</p> <p>*2/*3: A</p> <p>*3/*3: A</p>	<p>andardised. Publication bias was assessed by funnel plots only and results were not shown. Of the 39 studies in this meta-analysis, 18 were included in the meta-analysis of Jorgensen 2012, 7 in the meta-analysis of Yang 2013, 1 in the meta-analyses of Zhang 2024 and Zhang 2016, and none on the meta-analysis of Asiimwe 2020.</p> <p>Results:</p> <table border="1" data-bbox="531 383 1225 1435"> <thead> <tr> <th colspan="4">Dose in comparison with *1/*1 (n^{*1/*1} = 5,749):</th> </tr> <tr> <th>genotype</th> <th></th> <th></th> <th>95% CI</th> </tr> </thead> <tbody> <tr> <td rowspan="4">*1/*2 (30 studies) (n^{*1/*2} = 1,216)</td> <td></td> <td>-19.6%</td> <td>-17.4 - -21.9</td> </tr> <tr> <td>Whites</td> <td>-19.9%</td> <td>-17.4 - -22.4</td> </tr> <tr> <td>Whites, no interacting drugs</td> <td>-23.1%</td> <td>-11.0 - -35.1</td> </tr> <tr> <td>Whites, interacting drugs</td> <td>-19.0%</td> <td>-16.1 - -21.9</td> </tr> <tr> <td rowspan="4">*1/*3 (37 studies) (n^{*1/*3} = 759)</td> <td></td> <td>-33.7%</td> <td>-29.4 - -38.1</td> </tr> <tr> <td>Whites</td> <td>-35.1%</td> <td>-29.6 - -40.7</td> </tr> <tr> <td>Whites, no interacting drugs</td> <td>-40.9%</td> <td>-32.2 - -49.5</td> </tr> <tr> <td>Whites, interacting drugs</td> <td>-33.4%</td> <td>-25.1 - -41.7</td> </tr> <tr> <td rowspan="4">*2/*2 (14 studies) (n^{*2/*2} = 78)</td> <td></td> <td>-36.0%</td> <td>-29.9 - -42.0</td> </tr> <tr> <td>Whites</td> <td>-36.8%</td> <td>-28.5 - -45.1</td> </tr> <tr> <td>Whites, no interacting drugs</td> <td>-48.7%</td> <td>-36.3 - -61.2</td> </tr> <tr> <td>Whites, interacting drugs</td> <td>-33.7%</td> <td>-21.6 - -45.8</td> </tr> <tr> <td rowspan="4">*2/*3 (17 studies) (n^{*2/*3} = 81)</td> <td></td> <td>-56.7%</td> <td>-49.1 - -64.3</td> </tr> <tr> <td>Whites</td> <td>-58.0%</td> <td>-50.0 - -66.0</td> </tr> <tr> <td>Whites, no interacting drugs</td> <td>-42.0%</td> <td>-23.9 - -60.0</td> </tr> <tr> <td>Whites, interacting drugs</td> <td>-58.8%</td> <td>-47.5 - -70.1</td> </tr> <tr> <td rowspan="4">*3/*3 (7 studies) (n^{*3/*3} = 24)</td> <td></td> <td>-78.1%</td> <td>-72.0 - -84.3</td> </tr> <tr> <td>Whites</td> <td>-78.1%</td> <td>-72.0 - -84.3</td> </tr> <tr> <td>Whites, no interacting drugs</td> <td>-</td> <td></td> </tr> <tr> <td>Whites, interacting drugs</td> <td>-80.6%</td> <td>-73.8 - -87.3</td> </tr> </tbody> </table> <p>The heterogeneity between the studies was significant for *1/*3, *2/*3 and *3/*3.</p> <p>There were no indications for publication bias.</p> <p>The variables age, African ethnicity, Asian ethnicity, exclusion of interacting drugs, and target INR had no significant influence on the dose reduction per genotype. *1/*2, *1/*3 and *2/*2 showed a trend for a smaller dose reduction in studies with interacting drugs (p = 0.11-0.15). *2/*2 showed a trend for an increase in dose reduction with age (p = 0.07). *1/*2 showed a trend for an increase in dose reduction with the target INR (p = 0.13).</p>	Dose in comparison with *1/*1 (n ^{*1/*1} = 5,749):				genotype			95% CI	*1/*2 (30 studies) (n ^{*1/*2} = 1,216)		-19.6%	-17.4 - -21.9	Whites	-19.9%	-17.4 - -22.4	Whites, no interacting drugs	-23.1%	-11.0 - -35.1	Whites, interacting drugs	-19.0%	-16.1 - -21.9	*1/*3 (37 studies) (n ^{*1/*3} = 759)		-33.7%	-29.4 - -38.1	Whites	-35.1%	-29.6 - -40.7	Whites, no interacting drugs	-40.9%	-32.2 - -49.5	Whites, interacting drugs	-33.4%	-25.1 - -41.7	*2/*2 (14 studies) (n ^{*2/*2} = 78)		-36.0%	-29.9 - -42.0	Whites	-36.8%	-28.5 - -45.1	Whites, no interacting drugs	-48.7%	-36.3 - -61.2	Whites, interacting drugs	-33.7%	-21.6 - -45.8	*2/*3 (17 studies) (n ^{*2/*3} = 81)		-56.7%	-49.1 - -64.3	Whites	-58.0%	-50.0 - -66.0	Whites, no interacting drugs	-42.0%	-23.9 - -60.0	Whites, interacting drugs	-58.8%	-47.5 - -70.1	*3/*3 (7 studies) (n ^{*3/*3} = 24)		-78.1%	-72.0 - -84.3	Whites	-78.1%	-72.0 - -84.3	Whites, no interacting drugs	-		Whites, interacting drugs	-80.6%	-73.8 - -87.3	<p>lower, respectively. The impact of CYP2C9 genotype tended to be larger in patients without interacting drugs.'</p>
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and meta-analysis.
Genet Med
2005;7:97-104.
PubMed PMID:
15714076.
ref. 16, continuation

following 8 quality indicators were abstracted: adequate description of the study population; a clear description of study design and recruitment methods; case and/or control group definitions, inclusion and exclusion criteria; the proportion of recruited subjects included in the analysis and how excluded subjects were dealt with; description of genotyping methods used and quality control measures; appropriate blinding of investigators to study outcomes; a statement of how ethnicity was dealt with in study populations; and data ascertainment methods (e.g., medical records, self-report). Of the included studies, 1 described the quality control measures, reported how was dealt with ethnicity (population restriction) and reported on blinding (investigation blinded to genotype), 1 described the quality control measures, reported how was dealt with ethnicity (population restriction), but did not report on blinding, 1 described the quality control measures, but did neither report on how was dealt with ethnicity nor on blinding, 2 reported how was dealt with ethnicity (population restriction), but neither described the quality control measures nor reported on blinding, and the remaining 4 didn't describe the quality control measures, didn't report how was dealt with ethnicity, and didn't report on blinding. Meta-analyses were performed with a random-effects model, but the meta-analysis protocol was not registered prospectively. The search and selection strategy was transparent and the data extraction was standardised. Publication bias analysis was not performed. Of the 9 studies investigating warfarin dose in this meta-analysis, 6 were included in the meta-analysis of Lindh 2009, 7 in the meta-analysis of Jorgensen 2012, and none in the meta-analyses of Zhang 2024, Asiimwe 2020, and Zhang 2016. Of the 3 studies investigating bleeding in this meta-analysis, all were included in the meta-analyses of Yang 2013 and Jorgensen 2012, and 1 in the meta-analysis of Zhang 2024.

doses and a greater risk of bleeding.'

(*1/*2 +
*2/*2 +
*2/*3): C

Results:

*2-carrier in comparison with no *2:			
		95% CI	Value for no *2:
Dose (mg/day and %) (8 studies)	-0.85 = -17%	-1.11- -0.60 = -22- -12%	5.0 mg/day
Total bleeding (RR) (2 studies)	1.91	1.16-3.17	
There was no significant heterogeneity between the studies.			
Results were similar after exclusion of Highashi 2002 from the meta-analyses. In this study, the genotype frequencies were not in Hardy Weinberg equilibrium.			

(*1/*3 +
*2/*3 +
*3/*3): C

*3-carrier in comparison with no *3:			
		95% CI	Value for no *3:
Dose (mg/day and %) (8 studies)	-1.92 = -37%	-2.47- -1.37 = -48- -26%	5.2 mg/day
Total bleeding (RR) (3 studies)	1.77	1.07-2.91	
The heterogeneity between the studies was high for the dose.			

<p>ref. 16, continuation</p>	<p>(*1/*2 + *1/*3 + *2/*2 + *2/*3 + *3/*3): C</p>	<p>Results were similar after exclusion of Highashi 2002 from the meta-analyses. In this study, the genotype frequencies were not in Hardy Weinberg equilibrium.</p> <table border="1" data-bbox="531 203 1217 398"> <tr> <td colspan="3" data-bbox="531 203 1217 237">(*2- and/or *3-carrier) in comparison with (no *2 and *3):</td> </tr> <tr> <td data-bbox="531 237 903 271"></td> <td data-bbox="903 237 1035 271"></td> <td data-bbox="1035 237 1217 271">95% CI</td> </tr> <tr> <td data-bbox="531 271 903 333">Dose (mg/day and %) (7 studies)</td> <td data-bbox="903 271 1035 333">-1.71 = -27%</td> <td data-bbox="1035 271 1217 333">-2.20- -1.22</td> </tr> <tr> <td data-bbox="531 333 903 398">Total bleeding (RR) (2 studies)</td> <td data-bbox="903 333 1035 398">2.26</td> <td data-bbox="1035 333 1217 398">1.36-3.75</td> </tr> </table> <p>The heterogeneity between the studies was high for the dose</p> <p>Results were similar after exclusion of Highashi 2002 from the meta-analyses. In this study, the genotype frequencies were not in Hardy Weinberg equilibrium.</p>	(*2- and/or *3-carrier) in comparison with (no *2 and *3):					95% CI	Dose (mg/day and %) (7 studies)	-1.71 = -27%	-2.20- -1.22	Total bleeding (RR) (2 studies)	2.26	1.36-3.75																							
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<p>ref. 17 SmPC Coumadin (warfarin), USA, 14-08-17.</p>	<p>0</p> <p>*1/*2: AA *1/*3: A *2/*2: A *2/*3: A *3/*3: A</p>	<p>Dosing: The initial dose is influenced by:</p> <ul style="list-style-type: none"> • Clinical factors including age, race, body weight, sex, concomitant medications, and comorbidities • Genetic factors (CYP2C9 and VKORC1 genotypes) <p>Select the initial dose based on the expected maintenance dose, taking into account the above factors.</p> <p><i>Dosing Recommendations with Consideration of Genotype</i> Table 1 displays three ranges of expected maintenance Coumadin doses observed in subgroups of patients having different combinations of CYP2C9 and VKORC1 gene variants. If the patient's CYP2C9 and/or VKORC1 genotype are known, consider these ranges in choosing the initial dose. Patients with CYP2C9 *1/*3, *2/*2, *2/*3, and *3/*3 may require more prolonged time (>2 to 4 weeks) to achieve maximum INR effect for a given dosage regimen than patients without these CYP variants.</p> <p>Table 1: Three ranges of expected maintenance Coumadin daily doses (in mg) based on CYP2C9 and VKORC1 genotypes[†]</p> <table border="1" data-bbox="531 1189 1206 1341"> <thead> <tr> <th rowspan="2">VKOR C1</th> <th colspan="6">CYP2C9</th> </tr> <tr> <th>*1/*1</th> <th>*1/*2</th> <th>*1/*3</th> <th>*2/*2</th> <th>*2/*3</th> <th>*3/*3</th> </tr> </thead> <tbody> <tr> <td>GG</td> <td>5-7</td> <td>5-7</td> <td>3-4</td> <td>3-4</td> <td>3-4</td> <td>0.5-2</td> </tr> <tr> <td>AG</td> <td>5-7</td> <td>3-4</td> <td>3-4</td> <td>3-4</td> <td>0.5-2</td> <td>0.5-2</td> </tr> <tr> <td>AA</td> <td>3-4</td> <td>3-4</td> <td>0.5-2</td> <td>0.5-2</td> <td>0.5-2</td> <td>0.5-2</td> </tr> </tbody> </table> <p>[†]Ranges are derived from multiple published clinical studies. VKORC1 -1639G>A (rs9923231) variant is used in this table. Other co-inherited VKORC1 variants may also be important determinants of warfarin dose.</p> <p>Clinical Pharmacology: <i>Pharmacokinetics</i> CYP2C9, a polymorphic enzyme, is likely to be the principal form of human liver CYP450 that modulates the in vivo anticoagulant activity of warfarin. Patients with one or more variant CYP2C9 alleles have decreased S-warfarin clearance. The S-enantiomer exhibits 2 to 5 times more anticoagulant activity than the R-enantiomer in humans, but generally has a more rapid clearance. <i>Pharmacogenomics</i> The S-enantiomer of warfarin is mainly metabolized to 7-hydroxywarfarin by CYP2C9, a polymorphic enzyme. The variant alleles, CYP2C9*2 and CYP2C9*3, result in decreased in vitro CYP2C9 enzymatic 7-hydroxylation of S-warfarin. The frequencies of these alleles in Caucasians are approximately 11% and 7% for CYP2C9*2 and CYP2C9*3, respectively. Other CYP2C9 alleles associated with reduced enzymatic activity occur at lower frequencies, including *5, *6, and *11 alleles in populations of African ancestry and *5, *9, and *11 alleles in Caucasians.</p>	VKOR C1	CYP2C9						*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3	GG	5-7	5-7	3-4	3-4	3-4	0.5-2	AG	5-7	3-4	3-4	3-4	0.5-2	0.5-2	AA	3-4	3-4	0.5-2	0.5-2	0.5-2	0.5-2	
VKOR C1	CYP2C9																																				
	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3																															
GG	5-7	5-7	3-4	3-4	3-4	0.5-2																															
AG	5-7	3-4	3-4	3-4	0.5-2	0.5-2																															
AA	3-4	3-4	0.5-2	0.5-2	0.5-2	0.5-2																															

ref. 17, continuation	IM: A PM: A	VKORC1 and CYP2C9 gene variants generally explain the largest proportion of known variability in warfarin dose requirements. CYP2C9 and VKORC1 genotype information, when available, can assist in selection of the initial dose of warfarin.	
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Risk group	VKORC1 polymorphism, use of CYP2C9 inhibitors
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Comments:

- We only included meta-analyses of more than 5 studies in the risk analysis. Smaller meta-analyses and separate studies did not contribute enough to the evidence to be included.
- Dosing algorithms:
Ethnicity predicts CYP2C9 enzyme activity also independent of CYP2C9 genotype (Hatta FH et al. Differences in CYP2C9 genotype and enzyme activity between Swedes and Koreans of relevance for personalized medicine: role of ethnicity, genotype, smoking, age, and sex. OMICS 2015;19:346-53. PubMed PMID: 25977991). For this reason, only algorithms based on a predominantly White population are included. For patients with an African or (East-)Asian background, other algorithms might give better results. For patients with an African background, also other CYP2C9 alleles, such as *6, *8 and *11, should be taken into account. Examples of algorithms for patients with an African background can be found in Alzubiedi S et al, Pharmacogenetic-guided warfarin dosing algorithm in African-Americans, J Cardiovasc Pharmacol 2016;67:86-92, PubMed PMID: 26355760 and Hernandez W et al, Ethnicity-specific pharmacogenetics: the case of warfarin in African Americans, Pharmacogenomics J 2014;14: 223-8, PubMed PMID: 24018621). The algorithm of Ramirez 2012 below also includes data on African-Americans. Examples of algorithms for patients with an East-Asian background can be found in Wang D et al. Optimisation of warfarin-dosing algorithms for Han Chinese patients with CYP2C9*13 variants. Eur J Clin Pharmacol 2023;79:1315-20. PMID: 37458773, Li J et al. Impact of VKORC1, CYP2C9, CYP1A2, UGT1A1, and GGCX polymorphisms on warfarin maintenance dose: Exploring a new algorithm in South Chinese patients accept mechanical heart valve replacement. Medicine (Baltimore) 2022; 101:e29626. PMID: 35866816, Li J et al. Impact of VKORC1, CYP2C9, CYP1A2, UGT1A1, and GGCX polymorphisms on warfarin maintenance dose: Exploring a new algorithm in South Chinese patients accept mechanical heart valve replacement. Medicine (Baltimore) 2022; 101:e29626. PMID: 35866816, Xia X et al. To establish a model for the prediction of initial standard and maintenance doses of warfarin for the Han Chinese population based on gene polymorphism: a multicenter study. Eur J Clin Pharmacol 2022;78:43-51. PMID: 34453556, Tanaka T et al. Influence of Renal Impairment and Genetic Subtypes on Warfarin Control in Japanese Patients. Genes (Basel) 2021 28;12:1537. PMID: 34680932, Chen J et al, A pharmacogenetics-based warfarin maintenance dosing algorithm from Northern Chinese patients, PLoS One 2014;9: e105250, PubMed PMID: 25126975, and Choi JR et al, Proposal of pharmacogenetics-based warfarin dosing algorithm in Korean patients, J Hum Genet 2011;56:290-5, PubMed PMID: 21326313.
In addition, only algorithms based on at least 150 patients are included. Furthermore, only articles are included in which the equation describing the developed algorithm is given.
- Tomek A et al. Pharmacogenetic algorithm for predicting daily dose of warfarin in Caucasian patients of Czech origin. Drug Metab Pers Ther 2021;36:123-8. PMID: 33780197.
An algorithm for warfarin daily dose was developed based on data from Czech (White) patients on stable warfarin anticoagulation (derivation cohort: n = 175, validation cohort: n = 223). The minimum age limit was 50 years in the derivation cohort. There was no age limit in the validation cohort. The adjusted coefficient of determination (R²) was 72.4% in the derivation and 62.3% in the validation cohort (S). The algorithm had higher precision than other currently published algorithms R² of 31-62%. Similar precision in a predominantly White population was reported only by Wadelius 2009 (Swedish population—59%). The mean absolute error of prediction in the validation cohort was 1.57 ± 1.59 mg with a median of 1.12 mg. The mean absolute percentage error was 35.5% with a median 22.4% (SD 41.06). 48.6% of patients were correctly predicted within the range of ± 20% of the used daily dose. 88 patients out of 223 (39.3%) would be overdosed, i.e., predicted dose was higher than the actually used dose. However, only in 29.5% of the overdosed patients, there was an error of more than 2 mg and all of these patients used daily dose of warfarin higher than 5 mg. About 126 patients (56.5%) would be underdosed (a predicted dose lower than the actually used dose) in average by 1.41 ± 1.12 mg. In 46.8% of underdosed patients, the error was less than 2 mg. The model is less precise for patients under 50 years of age (n=61), with R²=38.8%. On the contrary, the prediction was sufficiently accurate for patients over 80 years of age (n=20)—52.7%. The coefficient of determination was 57.7% for patients with excess body weight (>100 kg, n=34) and due to the small number effect even 97.7% for patients with body weight under 50 kg (n=3).
The algorithm is:
 $\sqrt{\text{daily dose [mg]}} = (2.049 - (0.016 * \text{age [years]}) + (0.007 * \text{height [cm]}) + (0.004 * \text{weight [kg]}) - (0.227 * \text{number of CYP2C9*2 alleles}) - (0.296 * \text{number of CYP2C9*3 alleles}) - (0.340 * \text{number of VKORC1 -1639G alleles}) - (0.397 * \text{use of amiodarone [no=0, yes=1]})$.

- Pirmohamed M et al. A randomized trial of genotype-guided dosing of warfarin. *N Engl J Med* 2013;369: 2294-303. PubMed PMID: 24251363.
227 patients were randomly assigned to genotype-guided warfarin dosing and 228 patients to the control group. The control group received loading doses of 10-5-5 mg (≤ 75 years of age) or 5-5-5 mg (> 75 years of age). The mean percentage of time in the therapeutic range was significantly higher in the genotype-guided group than in the control group (67.4% and 60.3% respectively). There were significantly fewer incidences of excessive anticoagulation (INR ≥ 4.0) in the genotype-guided group. The median time to reach a therapeutic INR was significantly shorter in the genotype-guided group than in the control group (21 days and 29 days respectively).

The genotype-guided algorithms employed were:

- Maintenance dose, slightly modified IWPC model (IWPC, 2009):

$$\sqrt{\text{Dose (mg/week)}} = 5.6044 - 0.02614 \times \text{Age [in years]} + 0.0087 \times \text{Height [cm]} + 0.0128 \times \text{Weight [kg]} - 0.8677 \times \text{VKORC1 1173 CT} - 1.6974 \times \text{VKORC1 1173 TT} - 0.5211 \times \text{CYP2C9 } *1/*2 - 0.9357 \times \text{CYP2C9 } *1/*3 - 1.0616 \times \text{CYP2C9 } *2/*2 - 1.9206 \times \text{CYP2C9 } *2/*3 - 2.3312 \times \text{CYP2C9 } *3/*3 - 0.5503 \times \text{amiodarone}$$

- Initial doses (Avery et al, 2011):

Loading over three days was calculated as followed: $LD3 = D / (1 - \exp(-24k)) (1 + \exp(-24k) + \exp(-48k))$.

Where D was the IWPC predicted maintenance dose per day in mg.

k is the elimination rate constant for the CYP2C9 genotypes:

$$*1/*1 = 0.0189\text{h}^{-1}$$

$$*1/*2 = 0.0158\text{h}^{-1}$$

$$*1/*3 = 0.0132\text{h}^{-1}$$

$$*2/*2 = 0.0130\text{h}^{-1}$$

$$*2/*3 = 0.009\text{h}^{-1}$$

$$*3/*3 = 0.0075\text{h}^{-1}$$

A loading dose regimen was used where the loading dose was gradually reduced, i.e. Day 1 dose $>$ Day 2 dose $>$ Day 3 dose. This was derived from the difference between the predicted daily dose (D) and the 3-day loading dose (LD3) according to the following:

Loading on Day 1: $(LD3 - D) \times 1.5 + D$

Loading on Day 2: $((LD3 - D) \times 1 + D$

Loading on Day 3: $(LD3 - D) \times 0.5 + D$

- Dose revision on day 4 or 5 (slightly modified model by Lenzini et al, 2010):

$$\text{Dose (mg/week)} = \text{EXP} (3.10894 - 0.00767 \times \text{age} - 0.51611 \times \ln(\text{INR}) - 0.23032 \times \text{VKORC1 1173T} - 0.14745 \times \text{CYP2C9} *2 - 0.3077 \times \text{CYP2C9} *3 + 0.24597 \times \text{BSA} + 0.26729 \times \text{Target INR} - 0.1035 \times \text{amiodarone} + 0.0169 \times \text{dose}_{-2} + 0.02018 \times \text{dose}_{-3} + 0.01065 \times \text{dose}_{-4}).$$

Where INR is the INR on day 4 or 5.

Dose₋₂ is the dose given 2 days before the INR is measured, Dose₋₃ is the dose given 3 days before the INR is measured, and Dose₋₄ is the dose given 4 days before the INR is measured. Dose₋₄ is only available if the INR is measured on the 5th day.

Body surface area (BSA) is calculated according to the formula by Dubois & Dubois where $BSA = (\text{weight (kg)}^{0.425} \times \text{height (cm)}^{0.725}) / 139.2$.

- Ramirez AH et al. Predicting warfarin dosage in European-Americans and African-Americans using DNA samples linked to an electronic health record. *Pharmacogenomics* 2012;13:407-18. PubMed PMID: 22329724.

An algorithm for the maintenance dose of warfarin was developed based on data from 1022 European-Americans and 145 African-Americans. The algorithm explained 53% of dose variation in European-Americans and 41% of dose variation in African-Americans.

The algorithm is:

$$\log[\text{weekly warfarin dose}] = 5.9487517 - 0.0073436353 \times \text{race (AA=0,EA=1)} - 0.025161445 \times \text{age (in years)} + 0.058138499 \times \text{sex (F=0,M=1)} + 1.1848957 \times \text{bsa (kg/m}^2) + 0.068020571 \times \text{smoking status (nonsmoker=0, smoker=1)} + 0.058578086 \times \text{VTE indication (no=0,yes=1)} - 0.10646416 \times \text{atrial fibrillation indication (no=0, yes=1)} - 0.8142521 \times \text{amiodarone use (no=0,yes=1)} - 0.64877338 \times \text{CYP2C9} *2 (\text{wt=0,heterozygote=1, homozygote=2}) - 1.0601067 \times \text{CYP2C9} *3 (\text{wt=0,heterozygote=1,homozygote=2}) - 1.9737831 \times \text{CYP2C9} *6 (\text{wt=0, heterozygote=1,homozygote=2}) - 1.0622944 \times \text{CYP2C9} *8 (\text{wt=0,heterozygote=1,homozygote=2}) + 0.24749973 \times \text{CYP4F2 (wt=0,heterozygote=1,homozygote=2)} - 0.31996754 \times \text{CALU (wt=0,heterozygote=1, homozygote=2)} - 0.87262446 \times \text{VKORC1 (wt=0,heterozygote=1,homozygote=2)}$$

- Horne BD et al. Pharmacogenetic warfarin dose refinements remain significantly influenced by genetic factors after one week of therapy. *Thromb Haemost* 2012;107:232-40. PubMed PMID: 22186998.

An algorithm for the warfarin dose on day 6-11 of treatment was developed based on data from 1342 patients. The algorithm was validated in a separate retrospective cohort of 342 patients. The algorithm explained 69% of dose variation after about one week of therapy.

The algorithm is:

$$\text{dose (mg/week)} = \text{EXP} (2.59853 - 0.47578 \times \text{Treatment Response Index} - 0.17132 \times \text{VKORC1} - 0.23385 \times \text{CYP2C9} *3 - 0.10696 \times \text{CYP2C9} *2 - 0.00549 \times \text{Age in years} + 0.16491 \times \text{BSA} - 0.09091 \times \text{Simvastatin Use} - 0.251 \times \text{Fluvastatin Use} - 0.11994 \times \text{Amiodarone Use} + 0.3319 \times \text{Inducer Use} + 0.08796 \times \text{Target INR} -$$

$0.13902 \times \text{Stroke} + 0.01028 \times \text{Day of Therapy}$)

BSA = body surface area

treatment response index = $\ln(\text{INR}/\text{effective dose})$, with the effective dose calculated by summing weighted prior doses. The relative weights of doses that were prescribed 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 days ago in the effective dose calculation were 0.306, 0.804, 0.555, 0.357, 0.229, 0.149, 0.099, 0.067, 0.047, and 0.033, respectively.

- Avery PJ et al. A proposal for an individualized pharmacogenetics-based warfarin initiation dose regimen for patients commencing anticoagulation therapy. *Clin Pharmacol Ther* 2011;90:701-6. PubMed PMID: 22012312.
The European Pharmacogenetics of Anticoagulant Therapy (EU-PACT) study group developed an algorithm for the initiation dose of warfarin based on data from 671 patients. The initiation dose was calculated based on the half-life of S-warfarin for the different CYP2C9 genotypes (maintenance dose = initiation dose/($1 - e^{-kt}$)). The initiation dose was divided over 3 days to minimize the risk of INR exceeding the therapeutic range. Based on simulation, the initiation dose reduces the time to stable, therapeutic INR for patients with variant CYP2C9 alleles. According to the simulation, the time to stable, therapeutic INR was reduced for *3/*3 from approximately 30 days to 12.5 days, the latter being equal to the time to stable, therapeutic INR for *1/*1. The maintenance dose was calculated with a modification of the algorithm of the International Warfarin Pharmacogenetics Consortium (IWPC). The modified IWPC algorithm was adapted to the mainly White population in Europe by removing the ethnicity variable. In addition, drugs that induce warfarin metabolism were also omitted from the IWPC algorithm, because very few patients are treated with potent inducers. In addition, their inclusion in the algorithm would require information on the duration of treatment, because it takes at least 2–3 weeks to induce enzymes.
The modified IWPC algorithm is:
 $\sqrt{\text{Predicted maintenance dose (mg/week)}} = [5.6044 - 0.02614 \times \text{age (years)} + 0.0087 \times \text{height (cm)} + 0.0128 \times \text{weight (kg)} - 0.8677 (\text{VKORC1 -1639 GA}) - 1.6974 (\text{VKORC1 -1639 AA}) - 0.5211 (\text{CYP2C9 *1/*2}) - 0.9357 (\text{CYP2C9 *1/*3}) - 1.0616 (\text{CYP2C9*2/*2}) - 1.9206 (\text{CYP2C9*2/*3}) - 2.3312 (\text{CYP2C9*3/*3}) - 0.5503 (\text{amiodarone})]$.
The developed EU-PACT algorithm for the initiation dose is:
MD + x (day 1), MD + 2x/3 (day 2), MD + x/3 (day 3), in which:
 $x = \text{MD} * [1 / (1 - e^{-k*24}) - 1 - e^{-k*24} - e^{-k*48}] / [1/3 + 2/3 * e^{-k*24} + e^{-k*48}]$
MD = maintenance dose, k = elimination rate constant
*1/*1: k = 0.0189
*1/*2: k = 0.0158
*1/*3: k = 0.0132
*2/*2: k = 0.0130
*2/*3: k = 0.009
*3/*3: k = 0.0075
- Zamboni CF et al. VKORC1, CYP2C9 and CYP4F2 genetic-based algorithm for warfarin dosing: an Italian retrospective study. *Pharmacogenomics* 2011;12:15-25. PubMed PMID: 21174619.
An algorithm for the maintenance dose of warfarin was developed based on data from 274 patients. The algorithm was validated in a separate set of 91 patients. The algorithm explained 56–65% of dose variation, which was comparable to the performance of the algorithm of the International Warfarin Pharmacogenetics Consortium (57–63% of dose variation) in these patient groups.
The algorithm is:
 $\sqrt{\text{maintenance dose (mg/week)}} = 7.39764 - 0.02734 \times \text{age (years)} + 1.06287 \times \text{BSA (m}^2) - 1.04468 (\text{VKORC1 -1639 GA}) - 2.12117 (\text{VKORC1 -1639 AA}) - 0.78983 (\text{CYP2C9*1*2}) - 1.17138 (\text{CYP2C9*1*3}) - 1.81292 (\text{CYP2C9*2*2, *2*3 or *3*3}) - 0.46723 (\text{CYP4F2*1*3}) - 0.71528 (\text{CYP4F2*1*1})$
BSA = body surface area
- Wells PS et al. A regression model to predict warfarin dose from clinical variables and polymorphisms in CYP2C9, CYP4F2, and VKORC1: Derivation in a sample with predominantly a history of venous thromboembolism. *Thromb Res* 2010;125:e259-64. PubMed PMID: 20421126.
An algorithm for the maintenance dose of warfarin was developed based on data from 249 patients. The algorithm explained 58% of the dose variation.
The algorithm is:
Dose = 1.85 - 0.048 x Age (in years) + 0.041 x BMI + 0.05 x Height (in cm) - 0.73 (Less Exercise) - 1.13 (2C9*2 Hetero) - 2.09 (2C9*2 Homo) - 1.51 (2C9*3 Hetero) - 1.43 (VKORC1 -1639 GA) - 2.86 (VKORC1 -1639 AA) - 1.33 (4F2 CC) - 1.24 (4F2 CT) - 1.46 (Angiotensin II Receptor Antagonist) - 0.84 (β -Blocker).
Less exercise means that a patient's self-rated physical activity level is less than or much less than those of a similar age.
In the investigated patient population ACE inhibitors included losartan and candesartan and β -blockers included metoprolol, atenolol and bisoprolol.
- Lenzini P et al. Integration of genetic, clinical, and INR data to refine warfarin dosing. *Clin Pharmacol Ther* 2010;87:572-8. PubMed PMID: 20375999.

An algorithm for the warfarin dose after day 4-5 of treatment was developed based on data from 969 patients. The algorithm was validated in a separate set of 616 patients. The algorithm explained 42-63% of dose variation and performed better than an algorithm without genotypes (26-48% of dose variation).

The algorithm is:

Maintenance dose (mg/week) = EXP [3.10894 - 0.00767 × Age (in years) - 0.51611 × ln(INR) - 0.23032 × VKORC1-1639 G>A - 0.14745 × CYP2C9*2 - 0.3077 × CYP2C9*3 + 0.24597 × BSA + 0.26729 × Target INR - 0.09644 (African Origin) - 0.2059 (Stroke) - 0.11216 (Diabetes) - 0.1035 (Amiodarone Use) - 0.19275 (Flu-vastatin Use) + 0.0169 × Dose₂ + 0.02018 × Dose₃ + 0.01065 × Dose₄].

- International Warfarin Pharmacogenetics Consortium. Estimation of the warfarin dose with clinical and pharmacogenetic data. *N Engl J Med* 2009;360:753-64. PubMed PMID: 19228618.

An algorithm for the maintenance dose of warfarin was developed based on data from 4043 patients. The algorithm was validated in a separate set of 1009 patients. The algorithm explained 43-47% of dose variation. The International Warfarin Pharmacogenetics Consortium (IWPC) algorithm is:

$\sqrt{\text{maintenance dose (mg/week)}} = 5.6044 - 0.2614 \times \text{Age (in decades)} + 0.0087 \times \text{Height (in cm)} + 0.0128 \times \text{Weight (in kg)} - 0.8677 \text{ (VKORC1 -1639 A/G)} - 1.6974 \text{ (VKORC1 -1639 A/A)} - 0.4854 \text{ (VKORC1 genotype unknown)} - 0.5211 \text{ (CYP2C9 *1/*2)} - 0.9357 \text{ (CYP2C9 *1/*3)} - 1.0616 \text{ (CYP2C9 *2/*2)} - 1.9206 \text{ (CYP2C9 *2/*3)} - 2.3312 \text{ (CYP2C9 *3/*3)} - 0.2188 \text{ (CYP2C9 genotype unknown)} - 0.1092 \text{ (Asian race)} - 0.2760 \text{ (Black or African American)} - 0.1032 \text{ (Missing or Mixed race)} + 1.1816 \text{ (Enzyme inducer)} - 0.5503 \text{ (Amiodarone)}$
Use of an enzyme inducer means use of carbamazepine, phenytoin, rifampin or rifampicin.

- Wadelius M et al. The largest prospective warfarin-treated cohort supports genetic forecasting. *Blood* 2009;113:784-92. PubMed PMID: 18574025.

An algorithm for the maintenance dose of warfarin was developed based on data from 1523 patients. The algorithm was validated in a separate set of 181 patients. The algorithm explained 53-59% of dose variation. Body weight and height were not available in the cohort. Instead of these parameters sex is included in the algorithm as a substitute. In addition, drugs that decrease the effect of warfarin are not included in the algorithm, because too few were present in the cohort to get reliable results.

The Swedish Warfarin Genetics cohort (WARG) algorithm is:

$\sqrt{\text{maintenance dose (mg/week)}} = 9.46832 - 0.90112 \text{ (VKORC1 -1639 A/G)} - 2.01863 \text{ (VKORC1 -1639 A/A)} - 0.50836 \text{ (CYP2C9 *1/*2)} - 0.97546 \text{ (CYP2C9 *1/*3)} - 1.10204 \text{ (CYP2C9 *2/*2)} - 1.74761 \text{ (CYP2C9 *2/*3)} - 3.40061 \text{ (CYP2C9 *3/*3)} - 0.03686 \times \text{Age (in years)} - 0.27698 \text{ (Female sex)} - 0.06992 \times \text{number of drugs that increase INR}$.

- Gage BF et al. Use of pharmacogenetic and clinical factors to predict the therapeutic dose of warfarin. *Clin Pharmacol Ther* 2008;84:326-31. PubMed PMID: 18305455.

An algorithm for the maintenance dose of warfarin was developed based on data from 1015 patients. The algorithm was validated in a separate set of 292 patients. The algorithm explained 53-54% of dose variation (31% in African Americans).

The Warfarin Dose Refinement Collaboration algorithm is:

warfarin dose (mg/day) = exp [0.9751 - 0.3238 × VKOR3673G>A + 0.4317 × BSA - 0.4008 × CYP2C9*3 - 0.00745 × age - 0.2066 × CYP2C9*2 + 0.2029 × target INR - 0.2538 (amiodarone) + 0.0922 (smoker) - 0.0901 (African-American race) + 0.0664 (DVT/PE)]

DVT/PE = deep venous thrombosis or pulmonary embolism

- Sconce EA et al. The impact of CYP2C9 and VKORC1 genetic polymorphism and patient characteristics upon warfarin dose requirements: proposal for a new dosing regimen. *Blood* 2005;106:2329-33. PubMed PMID: 15947090.

An algorithm for the maintenance dose of warfarin was developed based on data from 297 patients. The algorithm was validated in a separate set of 38 patients. The algorithm explained 54% of dose variation.

The algorithm is:

$\sqrt{\text{Dose}} = 0.628 - 0.0135 \times \text{Age (in years)} - 0.240 \times \text{CYP*2} - 0.370 \times \text{CYP*3} - 0.241 \text{ (VKORC1 -1639 GG)} - 0.482 \text{ (VKORC1 -1639 GA)} - 0.723 \text{ (VKORC1 -1639 AA)} + 0.0162 \times \text{Height (in cm)}$.

- Cost effectiveness:

Cost effectiveness analyses in Thai, Chinese, and Indian patients were not included, because they do not add enough information about the cost effectiveness in a mainly White population.

QALY = quality adjusted life year

- Zhu Y et al. Systematic review of the evidence on the cost-effectiveness of pharmacogenomics-guided treatment for cardiovascular diseases. *Genet Med* 2020;22:475-86. PMID: 31591509.

The systematic review of cost-effectiveness studies showed supportive evidence for warfarin-CYP2C9/VKORC1. The authors conclude however, that this review identifies the need for further research on economic evaluations of PGx implementation.

Of the 16 studies[#] investigating cost-effectiveness of genotype-guided warfarin treatment, 7 studies (44%) concluded no cost-effectiveness or mixed evidence, particularly from the societal perspective. The authors conclude that implementing PGx-guided treatment approaches for atrium fibrillation patients receiving warfarin needs more careful evaluation from different perspectives.

[#] 1. Kim D-J et al. Cost Effectiveness of Genotype-Guided Warfarin Dosing in Patients with Mechanical Heart Valve Replacement Under the Fee-for-Service System. *Appl Health Econ Health Policy* 2017;15:657-667.

2. Verhoef 2016.
 3. Mitropoulou C et al. Economic evaluation of pharmacogenomic-guided warfarin treatment for elderly Croatian atrial fibrillation patients with ischemic stroke. *Pharmacogenomics* 2015;16:137-148.
 4. Janzic A, Kos M. Cost effectiveness of novel oral anticoagulants for stroke prevention in atrial fibrillation depending on the quality of warfarin anticoagulation control. *Pharmacoeconomics* 2015;33:395-408.
 5. You JHS. Pharmacogenetic-guided selection of warfarin versus novel oral anticoagulants for stroke prevention in patients with atrial fibrillation: a cost-effectiveness analysis. *Pharmacogenet Genomics*. 2014;24(1):6-14.
 6. Pink 2014.
 7. Chong HY et al. Cost-effectiveness analysis of pharmacogenetic-guided warfarin dosing in Thailand. *Thromb Res* 2014;134:1278-1284.
 8. Nshimyumukiza 2013.
 9. You JHS et al. Cost-effectiveness of dabigatran versus genotype-guided management of warfarin therapy for stroke prevention in patients with atrial fibrillation. *PLoS ONE*. 2012;7(6):e39640.
 10. Meckley LM, Gudgeon JM, Anderson JL, Williams MS, Veenstra DL. A policy model to evaluate the benefits, risks and costs of warfarin pharmacogenomic testing. *Pharmacoeconomics*. 2010;28(1):61-74.
 11. You 2009.
 12. Patrick 2009.
 13. Leey JA et al. Cost-effectiveness of genotype-guided warfarin therapy for anticoagulation in elderly patients with atrial fibrillation. *Am J Geriatr Pharmacother* 2009;7:197-203.
 14. Eckman 2009.
 15. McWilliam A et al.. Healthcare impact of personalized medicine using genetic testing: an exploratory analysis for warfarin. *Per Med* 2008;5:279-284.
 16. You JHS et al. The potential clinical and economic outcomes of pharmacogenetics-oriented management of warfarin therapy - A decision analysis. *Thrombosis and Haemostasis* 2004;92:590-597.
- Verhoef TI et al. Cost-effectiveness of pharmacogenetic-guided dosing of warfarin in the United Kingdom and Sweden. *Pharmacogenomics J* 2016;16:478-84. PMID: 27272045.
- For patients with atrial fibrillation from the UK and Sweden with mean ages of respectively 70.9 and 72.5 years, genotype guided warfarin therapy was more cost effective than standard care. The costs were £ 6,702 and 253,848 Swedish Kronor (SEK) per QALY gained, which is less than the thresholds of £ 20,000 and 500,000 SEK per QALY gained. The Swedish threshold of 500,000 SEK is approximately £ 40,000. In 93% of the simulations in the United Kingdom and 67% of the simulations in Sweden, the costs were lower than the thresholds.
- Lifelong medical costs were calculated. The calculations were based on a price of INR monitoring and visit to an anticoagulation clinic of £ 24.20 and 221 SEK, a price of warfarin of £ 3.20 and 45 SEK per month, a price of aspirin of £ 1.72 and 21 SEK per month, and costs for genotyping of £ 35.03 and 440 SEK. The percentage time within different INR ranges (<2.0, 2.0–3.0, 3.0–5.0 and >5.0) was derived from the EU-PACT trial (Pirmohamed M et al. A randomized trial of genotype-guided dosing of warfarin. *N Engl J Med* 2013;369:2294-303). The risks of adverse events associated with each of the four INR ranges were derived from a meta-analysis of 19 randomized trials and observational studies of vitamin K antagonists (Oake N et al. Anticoagulation intensity and outcomes among patients prescribed oral anticoagulant therapy: a systematic review and meta-analysis. *CMAJ* 2008; 179: 235–244). Thromboembolic events consisted mainly of ischaemic strokes, but 28% were assumed to be transient ischaemic attacks. Patients with a stroke were assumed to have a 10% chance of dying and a 47% chance of disability, while patients with a transient ischaemic attack were assumed to fully recover. The majority of haemorrhagic events (80%) were assumed to be extra-cranial haemorrhage. The risk that an intracranial haemorrhage would result in permanent disability was assumed to be 50% and the chance that it would be fatal 45%; these values were assumed to be zero for an extra-cranial haemorrhage. Patients were assumed to switch to aspirin after an intracranial haemorrhage. Event rates after 3 months were assumed to be the same in both types of warfarin therapy. The number of INR measurements in the first three months was derived from the EU-PACT trial. The authors assumed one measurement per month thereafter.
- Pharmacogenetic-guided dosing was cost-effective if genotyping costs would be no higher than £86 in the United Kingdom (given a cost-effectiveness threshold of £ 20,000 per QALY gained) or 809 SEK (approximately £64) in Sweden (given a threshold of 500 000 SEK).
- You JH. Universal versus genotype-guided use of direct oral anticoagulants in atrial fibrillation patients: a decision analysis. *Pharmacogenomics* 2015;16:1089-100. PubMed PMID: 26230572.
- For 65-year-old newly diagnosed atrial fibrillation patients with a high risk for stroke, a genotype guided therapy was more cost effective than direct oral anticoagulants for all patients (costs were 314,129 USD less per QALY gained, which is higher than the threshold of 50,000 USD/QALY). Genotype guided therapy consisted of warfarin for patients with normal warfarin sensitivity and a direct oral anticoagulant for patients with a genotype leading to high warfarin sensitivity (CYP2C9 *2 or *3 variants or VKORC1 -1639 A/A) or low warfarin sensitivity (VKORC1 -1639 G/G in combination with CYP2C9 *1/*1).
- Medical costs were calculated for a period of 35 years. For the genotype guided therapy the calculated costs were 124,568 USD and the calculated QALYs 10.6087. The calculation was based on a price of warfarin management (anticoagulation care with INR monitored at least monthly) of USD 34 per month, a price of

warfarin (dosage to be determined by the International Warfarin Pharmacogenetics Consortium (IWPC) algorithm) of USD 10.5 per month, a price of direct oral anticoagulants (dabigatran 150 mg twice daily, rivaroxaban 20 mg daily or apixaban 5 mg twice daily) of USD 173 per month, and genotyping costs of USD 80. Risk for clinical events and costs of genotyping were retrieved from literature. In the model, patients who survived a major haemorrhagic event would stop the current anticoagulation therapy and start on aspirin alone. Patient who survived a major thromboembolic event while receiving a direct oral anticoagulant would resume the initial anticoagulation therapy. Those who experienced a major thromboembolic event on warfarin would change to a direct oral anticoagulant. Out-of-range INR in patients receiving warfarin was defined as <1.8 or >3.2. A focused warfarin care system, leading to 81% of time within the therapeutic range was assumed.

Universal use of direct oral anticoagulants would become cost-effective if the monthly drug cost of direct oral anticoagulants was less than USD 30 (lower than the monthly drug cost and management cost of warfarin of USD 40) or if time in the therapeutic range of warfarin therapy was less than 67.8%. The two-way sensitivity analysis on these two variables demonstrated that if the time in the therapeutic range of warfarin was similar to the average anticoagulation control reported in clinical trials of direct oral anticoagulants versus warfarin (60% of time in the therapeutic range), the genotype guided therapy would remain the preferred strategy when direct oral anticoagulants cost more than USD 250 per month. When the monthly cost of direct oral anticoagulants declined to USD 30, a high percentage of time in the therapeutic range (81%) of warfarin should be achieved in order for the genotype guided therapy to be the preferred option. Extended sensitivity analysis on prevalence of normal warfarin sensitivity showed genotype guided therapy to be the preferred strategy in ethnic groups with prevalence of normal warfarin sensitivity >0.56%.

- Pink J et al. Cost-effectiveness of pharmacogenetics-guided warfarin therapy vs. alternative anticoagulation in atrial fibrillation. *Clin Pharmacol Ther* 2014;95:199-207. PubMed PMID: 24067746.

For the UK population of atrial fibrillation patients, apixaban was more cost effective than genotype guided warfarin therapy (costs were £ 19,858 per QALY gained, which is lower than the threshold of £ 20,000-30,000/QALY). Genotype guided warfarin therapy was more cost effective than not genotype guided warfarin therapy (costs were £ 13,226 per QALY gained). For both therapies, the initial warfarin doses were fixed (10 mg on day 1, 10 mg on day 2 and 5 mg on day 3) and IWPC algorithms were used. Neither dabigatran nor rivaroxaban were cost-effective options.

Lifelong medical costs were calculated. For the genotype guided therapy the calculated costs were £ 5,921 and the calculated QALYs 5.724. The calculation was based on a price of warfarin monitoring of £ 198.39 per year, a price of warfarin of £ 41.23 per year, a price of dabigatran (150 mg twice daily) of £ 919.80 per year, a price of rivaroxaban (20 mg daily) of £ 766.50 per year, a price of apixaban (5 mg twice daily) of £ 802.25 per year, a price of aspirin of £ 7.39 per year, and genotyping costs of £ 20.00. Drug costs were taken from the British National Formulary. Risk for clinical events were calculated from an indirect comparison of the trials of warfarin versus the direct oral anticoagulants (RE-LY, ROCKET-AF and ARISTOTLE). As indicated by You 2015, average anticoagulation control with warfarin in these trials is relatively low (60% of time in the therapeutic range). Event rates for genotype guided versus not genotype guided warfarin therapy were derived from literature. Event rates after 3 months were assumed to be the same in both types of warfarin therapy. In the model, patients who discontinued dabigatran, rivaroxaban, or apixaban because of a bleed or who discontinued warfarin for any reason were assumed to be switched to aspirin. Other discontinuing patients were switched to warfarin.

- Nshimyumukiza L et al. Dabigatran versus warfarin under standard or pharmacogenetic-guided management for the prevention of stroke and systemic thromboembolism in patients with atrial fibrillation: a cost/utility analysis using an analytic decision model. *Thromb J* 2013;11:14. PubMed PMID: 23866305.

For newly diagnosed atrial fibrillation patients with a mean age of 64 years, who never had a previous stroke, genotype guided warfarin therapy was less cost effective than standard warfarin therapy (costs were CAD\$ (Canadian dollar) 54,118 per QALY gained, which is higher than the threshold of CAD\$ 50,000 per QALY gained). Dabigatran 150 mg twice daily was more cost effective than standard warfarin therapy (costs were CAD\$ 4,765 per QALY gained).

Medical costs were calculated for the first 5 years of therapy. For the genotype guided therapy the calculated costs were CAD\$ 7,749 and the calculated QALYs 3.5453. The calculation was based on a price of INR monitoring in the first year of CAD\$ 8.06 per month for standard warfarin therapy and CAD\$ 5 per month for genotype guided warfarin therapy, a price of INR monitoring in subsequent years of CAD\$ 4.03 per month, a price of warfarin 5 mg/day of CAD\$ 0.074 per day, a price of dabigatran of CAD\$ 3.20 per day, and genotyping costs of CAD\$ 615. For the standard warfarin therapy, the time spent in each INR category (below, within or above the therapeutic range) was based on the results of the RE-LY clinical trial comparing dabigatran and warfarin (Connolly 2009), while for the genotype guided warfarin therapy, it was calculated using data from the Couma-Gen trial, which compares genotype guided therapy with standard therapy (Anderson JL et al. Randomized trial of genotype-guided versus standard warfarin dosing in patients initiating oral anticoagulation. *Circulation* 2007;116:2563-70). This means that the data for standard warfarin therapy and the relative effect of genotype guided warfarin therapy were derived from different trials and patient groups. In the RE-LY trial, patients from 44 different countries participated. The Couma-Gen trial studied only patients from the United States. It was assumed that after one year 100% of individuals, whatever the warfarin group they belong to, had reached a stable maintenance dose.

Genotype guided warfarin therapy would be more cost effective than standard warfarin therapy and dabigatran, if it would change the average patient time in the therapeutic range in the first year from 66.6% to 76.8%, i.e. an increase with 20%. In this case, the costs per QALY gained for genotype guided warfarin

therapy would be CAD\$ 3,250. In the Couma-Gen trial, genotype guided therapy increased the time in the therapeutic range with 7.3%.

With a threshold of CAD\$ 50,000 per QALY gained, dabigatran was more cost-effective than standard warfarin therapy in 99.75% of simulations.

- Patrick AR et al. Cost-effectiveness of genotype-guided warfarin dosing for patients with atrial fibrillation. *Circ Cardiovasc Qual Outcomes* 2009;2:429-36. PubMed PMID: 20031873.

For 70-year-old patients with newly-diagnosed atrial fibrillation, genotype guided warfarin therapy was more cost effective than usual care only if it reduces out-of-range international normalized ratio values by more than 5 to 9 percentage points (costs respectively less than 100,000 and 50,000 USD per QALY gained). The midpoint of the result of 2 published randomized controlled trials of genetically-guided dosing was 8.5% more time spent in the therapeutic range.

Medical costs were calculated for the life expectancy of 11.42 years. The calculations were based on a price of INR monitoring (assumed: 8 INR tests during the first month of treatment and 1 in each subsequent month) of USD 29, a price of warfarin (average dose of 5 mg/day) of USD 71 per 3 months, and costs for genotyping and blood sample collection of USD 575. Risks for clinical events were retrieved from literature. Event rates after 3 months were assumed to be the same in both types of warfarin therapy.

Variation of input data resulted in 42% of scenarios being cost effective at a threshold of 50,000 USD/QALY and 70% at a threshold of 100,000 USD/QALY. Genotyping was more cost-effective in younger patients, with the costs increasing from USD 29,000 per QALY in 50-year-old patients to USD 120,000 per QALY in 85-year-old patients. Test costs and assumptions about the rate of major bleeding during treatment initiation also influenced the results, because this parameter affected the number of bleeding events that could be averted through genotyping. In addition, the amount of patient time shifted from high INR to therapeutic INR influenced the cost effectiveness.

- Meckley LM et al. A policy model to evaluate the benefits, risks and costs of warfarin pharmacogenomics testing. *Pharmacoeconomics* 2010;28:61-74. PubMed PMID: 20014877.

For 65-year-old atrial fibrillation patients starting with warfarin, genotype guided therapy was less cost effective than usual care (costs were 60,725 USD more per QALY gained, which is higher than the threshold of 50,000 USD/QALY). Varying of the input parameters resulted in 46% of simulations with additional costs for genotype guided therapy of less than 50,000 USD/QALY.

Lifelong medical costs were calculated. For the genotype guided therapy the calculated costs were 46,970 USD and the calculated QALYs 12.0851. The calculation was based on a price of warfarin therapy of USD 63 per year and genotyping costs of USD 175. Risk for clinical events were mostly based on INR differences observed in the Couma-Gen trial in which the use of a pharmacogenetic maintenance dose algorithm to select initial warfarin dose was compared with standard care via an anticoagulation specialist pharmacist (n = 200). The effect of CYP2C9 on bleeding risk was retrieved from the meta-analysis of Sanderson 2005. Event rates after 6 months were assumed to be the same in both types of warfarin therapy.

Results were most sensitive to the cost of genotyping and the effect of genotyping. If the genotyping test costs less than USD 13, then pharmacogenomic testing would be a cost-saving strategy. If data from the Caraco trial (n = 283) were used instead of data from the Couma-Gen trial, or pharmacogenomic initiation further reduced bleeds in the CYP2C9 variant patients, pharmacogenomic warfarin initiation would be cost saving. Changes to some key structural assumptions increased the additional costs to more than USD 100,000 per QALY.

The costs and benefits of genotype guided therapy were not evenly distributed between the different genotypes. For patients that were both VKORC1 and CYP2C9 wild-type, the costs increased with USD 13,500/QALY due to a reduction in bleeds (despite higher doses), thromboembolism and deaths. For CYP2C9 variant patients the reduction in bleeds was offset by the increased number of thromboembolic events, resulting in reduced QALYs. These results imply that CYP2C9 variant patients may be more challenging to manage, even once their genetic status is known. This is potentially the result of a significantly slower therapeutic response in these patients due to the decreased rate of drug metabolism.

- You JH et al. Potential clinical and economic outcomes of CYP2C9 and VKORC1 genotype-guided dosing in patients starting warfarin therapy. *Clin Pharmacol Ther* 2009;86:540-7. PubMed PMID: 19571807.

For patients starting with warfarin, genotype guided therapy was less cost effective than usual care (costs were 347,059 USD more per QALY gained, which is higher than the threshold of 50,000 USD/QALY). Varying of the input parameters resulted in 48% of simulations with additional costs for genotype guided therapy of less than 50,000 USD/QALY.

Medical costs for the first year of treatment were calculated. The calculation was based on a price of anticoagulation clinic care of USD 303 per year and genotyping costs of USD 200. Risk for clinical events were based on INR differences observed in the Couma-Gen trial in which the use of a pharmacogenetic maintenance dose algorithm to select initial warfarin dose was compared with standard care via an anticoagulation specialist pharmacist (n = 200).

Results were most sensitive to the cost of genotyping, the relative percentage reduction in out-of-range INRs in the genotype guided dosing group, and the percentage of out-of-range INRs in the standard dosing group.

- Eckman MH et al. Cost-effectiveness of using pharmacogenetic information in warfarin dosing for patients with nonvalvular atrial fibrillation. *Ann Intern Med* 2009;150:73-83. PubMed PMID: 19153410.

For male patients aged 69 years with nonvalvular atrial fibrillation at average risk for stroke and without specific risk factors for bleeding, genotype guided dosing was less cost effective than usual care (costs were 171,800 USD more per QALY gained, which is higher than the threshold of 50,000 USD/QALY). Varying of

the input parameters resulted in 10% of simulations with additional costs for genotype guided therapy of less than 50,000 USD/QALY. For genetic testing to cost less than USD 50,000 per QALY, it would have to be restricted to patients at high risk for haemorrhage or meet the following criteria: prevent greater than 32% of major bleeding events, be available within 24 hours, and cost less than \$200.

Life-long medical costs were calculated. For the genotype guided therapy the calculated costs were 19,684 USD and the calculated QALYs 7.5780. The calculation was based on a price of warfarin of USD 36.99 per month, genotyping costs of USD 400 and a 3-day delay in initiating warfarin therapy due to genotyping. The relative risk for major bleeding in the genotype guided versus standard warfarin therapy (0.68; 95% CI: 0.22-2.06) was calculated from a meta-analysis of the 3 trials comparing both types of therapy ($n_{\text{total}} = 429$). Major bleeding rates after 1 month were assumed to be the same in both types of warfarin therapy.

Results were most sensitive to the cost of genotyping and the delay in warfarin therapy due to genotyping. If the cost of genotyping was less than USD 140, genotype guided dosing would be cost effective (additional costs less than USD 50,000/QALY). If the cost of genotyping was less than USD 40, genotype guided dosing would be cost saving. If there were no delay in initiating treatment, the additional costs would be USD 116,000/QALY. In the scenario where in-hospital genotyping would be possible, with cost of genotyping of USD 200 and the results available in 24 hours, allowing immediate initiation of warfarin therapy, the additional costs of genotype-guided dosing would be USD 51,000/QALY.

- Existing guideline:

Johnson JA et al. Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C9 and VKORC1 genotypes and warfarin dosing. *Clin Pharmacol Ther* 2011;90:625-9. PubMed PMID: 21900891 and Johnson JA et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for pharmacogenetics-guided warfarin dosing: 2017 update. *Clin Pharmacol Ther* 2017;102:397-404. PMID: 28198005.

CPIC indicates that common variants in CYP2C9, VKORC1, and CYP4F2 account for up to 18%, 30%, and 11% respectively, of the variance in stable warfarin dose among patients of European ancestry (Limdi NA et al. Warfarin pharmacogenetics: a single VKORC1 polymorphism is predictive of dose across 3 racial groups. *Blood*. 2010; 115:3827–34. PubMed: 20203262; Gage BF et al. Use of pharmacogenetic and clinical factors to predict the therapeutic dose of warfarin. *Clin Pharmacol Ther* 2008;84:326-31. PubMed: 18305455; Klein TE et al. Estimation of the warfarin dose with clinical and pharmacogenetic data. *N Engl J Med* 2009; 360:753-64. PubMed: 19228618; Wadelius M et al. The largest prospective warfarin-treated cohort supports genetic forecasting. *Blood* 2009;113:784-92. PMID: 18574025; and Liang R et al. Influence of CYP4F2 genotype on warfarin dose requirement—a systematic review and meta-analysis. *Thromb Res* 2012;130:38-44. PubMed: 22192158), but that because of differing allele frequencies across populations, these variants explain less of the dose variability in patients of other ancestries. In particular, CYP2C9*2 is virtually absent in Asians, and additional CYP2C9 alleles (e.g. *5, *6, *8, and *11 alleles) occur almost exclusively in persons of African ancestry and contribute to dose variability in this population.

CPIC indicates that in vitro and in vivo studies suggest that CYP2C9*2 and *3 impair metabolism of S-warfarin by ~30-40% and ~80-90%, respectively (Lee CR et al. Cytochrome P450 2C9 polymorphisms: a comprehensive review of the in-vitro and human data. *Pharmacogenetics* 2002;12:251-63. PMID: 11927841). In addition, CPIC indicates that compared to patients homozygous for CYP2C9*1, individuals who inherit one or two copies of CYP2C9*2 or *3 are at greater risk of bleeding during warfarin therapy (Aithal GP et al. Association of polymorphisms in the cytochrome P450 CYP2C9 with warfarin dose requirement and risk of bleeding complications. *Lancet* 1999;353:717-9. PMID: 10073515 and Mega JL et al. Genetics and the clinical response to warfarin and edoxaban: findings from the randomised, double-blind ENGAGE AF-TIMI 48 trial. *Lancet* 2015;385:2280-7. PMID: 25769357), require lower doses to achieve similar levels of anticoagulation, and require more time to achieve a stable INR (Aithal 1999) (referring to CPICs table with publications providing evidence linking CYP2C9 to warfarin phenotype). Finally, CPIC indicates that additional CYP2C9 alleles (CYP2C9*5, *6, *8, and *11) are associated with decreased function of the CYP2C9 enzyme and contribute to dose variability. These alleles are found with the highest frequency among those of African ancestry, and collectively are more common than CYP2C9*2 and *3 in that population (CPICs CYP2C9 frequency table and Gene Reference Materials for CYP2C9. 2016. <<https://www.pharmgkb.org/page/cyp2c9RefMaterials>> [Accessed November 4, 2016]).

CPIC mentions three randomised controlled trials examining the efficacy of genotype-guided warfarin dosing (Pirmohamed M et al. A randomized trial of genotype-guided dosing of warfarin. *N Engl J Med* 2013; 369:2294–303. PubMed: 24251363 (EU-PACT trial); Kimmel SE et al. A pharmacogenetic versus a clinical algorithm for warfarin dosing. *N Engl J Med* 2013;369: 2283–93. PubMed: 24251361 (COAG trial); and Gage BF et al. Effect of genotype-guided warfarin dosing on clinical events and anticoagulation control among patients undergoing hip or knee arthroplasty: the GIFT randomized clinical trial. *JAMA* 2017;318(12):1115-1124. PMID: 18574025 (GIFT trial)) These randomised controlled trials were also included in the meta-analyses of trials comparing genotype-guided with not genotype-guided therapy in this risk analysis when they were already published at the time the meta-analysis was performed. CPIC indicates that genotype-guided dosing was based on VKORC1 and CYP2C9 *2 and *3 in the EU-PACT and COAG trials and in addition on CYP4F2*3 in the GIFT trial. CPIC indicates that the EU-PACT trial, that was conducted in a homogenous European population, showed shorter time to stable dose, improved percent time in therapeutic range, and reduced number of episodes with an INR>4 using a pharmacogenetic dosing algorithm compared to standard dosing. CPIC indicates that the COAG trial, that was conducted in an ethnically diverse cohort with 27% of participants of African ancestry, overall did not show a difference in time to stable dose, percent time in therapeutic range, reduction in number of episodes with INR >4 or <2, or bleeding risk with a pharmacogenetic dosing algorithm compared to a clinical algorithm. In non-blacks, the pharmacogenetic dosing algorithm arm had more patients whose stable dose was within 1 mg per day of the algorithm-predicted

dose (57 vs 39%, respectively). In contrast, the pharmacogenetic dosing algorithm was less accurate at predicting within 1 mg/day of the stable dose than the clinical algorithm in blacks (38 vs 48% respectively). Blacks were more likely to have an INR above range with pharmacogenetic dosing, which could be due to other variants that influence warfarin dose and are more common in blacks (i.e., CYP2C9*5, *6, *8, and *11) not being genotyped in the COAG trial. Other variants that influence warfarin dose and are more common in blacks (i.e., CYP2C9*5, *6, *8, and *11 and CYP2C rs12777823) were not genotyped in the COAG trial and their absence likely led to significant overdosing in patients with these alleles (Limdi 2010, Drozda K et al. Poor warfarin dose prediction with pharmacogenetic algorithms that exclude genotypes important for African Americans. *Pharmacogenet Genomics* 2015;25:73-81. PMID: 25461246). Consequently, CPIC recommends against pharmacogenetic dosing of warfarin in blacks when only CYP2C9*2 and *3 genotype results are available. CPIC indicates that the GIFT trial, that was conducted in orthopaedic patients, showed a 27% reduction in the composite outcome (including symptomatic and asymptomatic venous thromboembolism, major haemorrhage, INR \geq 4, and death) with genotype-guided versus clinical algorithm dosing.

Recommendations for adults

CPIC indicates that the recommendations for dosing based on genotype are derived from numerous observational and prospective studies, and randomised trials that suggest the ability to more accurately identify stable therapeutic warfarin dose requirements through use of both genetic and clinical information. However, CPIC indicates that data from prospective studies and randomised controlled trials are equivocal on whether the improvement in dosing prediction by pharmacogenetics dosing leads to improved clinical outcomes. Furthermore, CPIC indicates that the majority of the literature underpinning these guidelines arises from individuals of European ancestry, African Americans, and East Asians, but that the more limited literature in other populations generally suggests the guidelines are appropriate in them also.

CPIC indicates that numerous studies have derived warfarin dosing algorithms that use both genetic and non-genetic factors to predict warfarin dose (Gage 2008; International Warfarin Pharmacogenetics Consortium 2009; and Lenzi 2010 and Avery 2011 (see Pirmohamed 2013)). CPIC indicates that the Gage and IWPC algorithms, created using more than 5000 subjects, perform well in estimating stable warfarin dose, although more recent data suggest they do not perform acceptably in African Americans when used without modification for CYP2C9 alleles frequently found in the African population (Kimmel 2013). These algorithms or minor adjustments to them have also been the algorithms used in both randomised controlled trials and most of the prospective dosing studies. CPIC indicates that dosing algorithms using genetic information outperform non-genetic clinical algorithms and fixed-dose approaches in dose prediction, except in African Americans when the algorithm only includes CYP2C9*2 and *3 (Gage 2008; International Warfarin Pharmacogenetics Consortium 2009; Kimmel 2013). Furthermore, CPIC indicates that genetics-based algorithms also better predict warfarin dose than the FDA-approved warfarin label table (Finkelman BS et al. Genetic warfarin dosing: tables versus algorithms. *J Am Coll Cardiol* 2011;57:612-8. PubMed: 21272753). CPIC refers to the EU-PACT trial (Pirmohamed 2013) for a pharmacogenetics-based warfarin initiation (loading) dose algorithm. Finally, CPIC indicates that it is important to note that these algorithms do not include CYP4F2, CYP2C9*5, *6, *8, or *11 or CYP2C rs12777823, and incorporation of CYP2C9*5, *6, *8, and *11 should be added to the algorithms when results are available. CPIC proposes to decrease the calculated dose by 15-30% in carriers of CYP2C9*5, *6, *8, or *11 (e.g. *1/*8, *1/*11, *8/*11). CPIC classifies this recommendation as moderate in patients of African ancestry and as optional in patients of non-African ancestry (see the tables below). CPIC indicates that the warfarindosing.org website contains both algorithms, the Gage algorithm as the primary algorithm and the IWPC algorithm as the secondary algorithm and can adjust for CYP4F2, CYP2C9*5 and *6. If utilizing warfarindosing.org, the user should be clear on whether the algorithm is or is not incorporating genotypes beyond CYP2C9 *2 and *3 and VKORC1, which are the only three genotypes in the original version of both algorithms.

VKORC1 and CYP2C9*2 and *3 genotype not available:

Recommendation	Strength of the recommendation
Dose clinically. ^a	Not mentioned.

^a "Dose clinically" means to dose without genetic information, which may include use of a clinical dosing algorithm or standard dose approach.

VKORC1 and CYP2C9*2 and *3 genotype available and non-African ancestry^a:

Recommendations	Strength of the recommendation
Calculate dose based on validated published pharmacogenetic algorithms. ^{b,c}	Strong ^d
For loading dose, a pharmacogenetics-based warfarin initiation dose algorithm ^e could be considered.	Optional ^f
Carriers of CYP2C9*5, *6, *8 or *11 variant alleles (e.g. *1/*8, *1/*11, *8/*11): Decrease calculated dose by 15-30%. ^g	Optional ^f
Carriers of CYP4F2 rs2108622 T allele: Increase dose by 5-10%.	Optional ^f

^a Data strongest for European and East Asian ancestry populations and consistent in other populations.

^b Most algorithms are developed for the target INR 2-3.

^c Consider an alternative agent in individuals with genotypes associated with CYP2C9 poor metabolism (e.g., CYP2C9*3/*3, *2/*3, *3/*3) or both increased sensitivity (VKORC1 A/G or A/A) and CYP2C9 poor metabolism.

^d Strong indicates that "The evidence is high quality and the desirable effects clearly outweigh the undesirable effects."

- ^e See the EU-PACT trial for pharmacogenetics-based warfarin initiation (loading) dose algorithm (Pirmohamed 2013).
- ^f Optional indicates that the desirable effects are closely balanced with undesirable effects, or the evidence is weak or based on extrapolations. There is room for differences in opinion as to the need for the recommended course of action.
- ^g Larger dose reduction might be needed in variant homozygotes (i.e. 20-40%).

*VKORC1 and CYP2C9*2 and *3 genotype available and African ancestry.*

	Recommendations	Strength of the recommendation
CYP2C9*5, *6, *8, and *11 not tested ^a	Dose clinically. ^b	Not mentioned.
CYP2C9*5, *6, *8, and *11 also tested	1. VKORC1-1639G>A and CYP2C9*2 and *3: Calculate dose based on validated published pharmacogenetic algorithms. ^{c,d} 2. Carriers of CYP2C9*5, *6, *8 or *11 variant alleles (e.g. *1/*8, *1/*11, *8/*11): Decrease calculated dose by 15-30%. ^f	Moderate ^e
	If African American ^g and tested to be a carrier of CYP2C rs1277623 A: Decrease dose by 10-25%.	Moderate ^e
	For loading dose, a pharmacogenetics-based warfarin initiation dose algorithm ^h could be considered.	Optional ⁱ

- ^a 45-50% of individuals with self-reported African ancestry carry CYP2C9*5,*6,*8,*11, or rs12777823. IF CYP2C9*5, *6, *8, and *11 WERE NOT TESTED, DOSE WARFARIN CLINICALLY. Note: these data derive primarily from African Americans, who are largely from West Africa. It is unknown if the same associations are present for those from other parts of Africa.
- ^b "Dose clinically" means to dose without genetic information, which may include use of a clinical dosing algorithm or standard dose approach.
- ^c Most algorithms are developed for the target INR 2-3.
- ^d Consider an alternative agent in individuals with genotypes associated with CYP2C9 poor metabolism (e.g., CYP2C9*3/*3, *2/*3, *3/*3) or both increased sensitivity (VKORC1 A/G or A/A) and CYP2C9 poor metabolism.
- ^e Moderate indicates that "There is a close or uncertain balance" as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.
- ^f Larger dose reduction might be needed in variant homozygotes (i.e. 20-40%).
- ^g African American refers to individuals mainly originating from West Africa.
- ^h See the EU-PACT trial for pharmacogenetics-based warfarin initiation (loading) dose algorithm (Pirmohamed 2013) with the caveat that the loading dose PG algorithm has not been specifically tested or validated in populations of African ancestry.
- ⁱ Optional indicates that the desirable effects are closely balanced with undesirable effects, or the evidence is weak or based on extrapolations. There is room for differences in opinion as to the need for the recommended course of action.

Recommendations for children

CPIC indicates that there is strong evidence for the use of CYP2C9*2 and *3 and VKORC1-1639G>A genotype to guide warfarin dosing in children of European ancestry. However, CPIC indicates that the studies in Japanese paediatric individuals are conflicting as VKORC1 and CYP2C9 could not be adequately evaluated due to the low numbers of CYP2C9 variant carriers, and that for other ethnicities, there is no evidence documenting that VKORC1 and CYP2C9 are important. Furthermore, CPIC indicates that there are no data in children that included CYP2C9*5, *6, *8, or *11 genotyping. Based on the current evidence, CPIC recommends to calculate warfarin dosing in children of European ancestry and if CYP2C9*2 and *3 and VKORC1-1639 genotype are available based on a validated published paediatric pharmacogenetic algorithm (Hamberg AK et al. Warfarin dose prediction in children using pharmacometric bridging--comparison with published pharmacogenetic dosing algorithms. Eur J Clin Pharmacol 2013;69:1275-83. PubMed: 23307232; and Biss TT et al. VKORC1 and CYP2C9 genotype and patient characteristics explain a large proportion of the variability in warfarin dose requirement among children. Blood 2012;119:868-73. PubMed: 22010099). A dosing tool that can be used in children of European ancestry is available at <http://www.warfarindoserevision.com> (Hamberg AK et al. Characterizing variability in warfarin dose requirements in children using modelling and simulation. Br J Clin Pharmacol 2014;78:158-69. PubMed: 24330000). CPIC considers the strength of this recommendation to be moderate (i.e. "There is a close or uncertain balance" as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.) CPIC recommends to dose clinically if CYP2C9*2 and *3 and VKORC1-1639 genotype are not available and in children of non-European ancestry. CPIC does not mention a strength for this recommendation.

Other considerations

CPIC indicates that, given that the CYP2C9 variant alleles are associated with reduced warfarin clearance, CYP2C9 genotype may influence time to onset and offset of anticoagulation, as measured by INR (Hamberg AK et al. A pharmacometric model describing the relationship between warfarin dose and INR response with respect to variations in CYP2C9, VKORC1, and age. Clin Pharmacol Ther 2010;87:727-34. PMID: 20410877).

On 4-6-2025, there was not a more recent version of the recommendations present on the CPIC-site.

Date of the literature search: 5 February 2025.

	Genotype	Code	Gene-drug interaction	Action	Date
	*1/*2	4 A	yes	no	29 September 2025

KNMP Pharmacogenetics Working Group decision	*1/*3	4 D	yes	yes
	*2/*2	3 A	yes	yes
	*2/*3	3 C	yes	yes
	*3/*3	4 C	yes	yes
	IM	3 A	yes	yes
	PM	3 A	yes	yes

Mechanism:

Warfarin consists of a racemic mixture. S-warfarin is a more potent anticoagulant than R-warfarin. S-warfarin is predominantly metabolized by CYP2C9, whereas R-warfarin is mainly metabolized by other enzymes.

Clinical Implication Score:

Table 1: Definitions of the available Clinical Implication Scores

Potentially beneficial	PGx testing for this gene-drug pair is potentially beneficial. Genotyping can be considered on an individual patient basis. If, however, the genotype is available, the DPWG recommends adhering to the gene-drug guideline	0-2 +
Beneficial	PGx testing for this gene-drug pair is beneficial. It is advised consider genotyping the patient before (or directly after) drug therapy has been initiated to guide drug and dose selection	3-5 +
Essential	PGx testing for this gene-drug pair is essential for drug safety or efficacy. Genotyping must be performed before drug therapy has been initiated to guide drug and dose selection	6-10 +

Table 2: Criteria on which the attribution of Clinical Implication Score is based

Clinical Implication Score Criteria	Possible Score	Given Score
Clinical effect associated with gene-drug interaction (drug- or diminished efficacy-induced)		
• CTCAE Grade 3 or 4 (clinical effect score D or E)	+	+
• CTCAE Grade 5 (clinical effect score F)	++	
Level of evidence supporting the associated clinical effect grade ≥ 3		
• One study with level of evidence score ≥ 3	+	+
• Two studies with level of evidence score ≥ 3	++	
• Three or more studies with level of evidence score ≥ 3	+++	
Number needed to genotype (NNG) in the Dutch population to prevent one clinical effect grade ≥ 3		
• $100 < \text{NNG} \leq 1000$	+	
• $10 < \text{NNG} \leq 100$	++	++
• $\text{NNG} \leq 10$	+++	
PGx information in the Summary of Product Characteristics (SmPC)		
• At least one genotype/phenotype mentioned	+	+
OR		
• Recommendation to genotype	++	
OR		
• At least one genotype/phenotype mentioned as a contra-indication in the corresponding section	++	
Total Score:	10+	5+
Corresponding Clinical Implication Score:		Beneficial