VKORC1: phenprocoumon 1911/1912

AA = homozygous allele variant (= -1639 AA = 1173 TT) (strongly increased coumarin sensitivity), Cl_{or} = oral clearance, mean = (weighted) mean, GA = heterozygous (= -1639 GA = 1173 CT) (increased coumarin sensitivity), GG = homozygous wild-type allele (= -1639 GG = 1173 CC) (normal coumarin sensitivity), HR = hazard ratio, INR = international normalised ratio, NS = non-significant, RR = relative risk, risk ratio, S = significant, SmPC = Summary of Product Characteristics, $t_{1/2}$ = half-life, VKORC1 = vitamin K epoxide reductase complex subunit 1

Disclaimer: The Pharmacogenetics Working Group of the KNMP formulates the optimal recommendations for each phenotype group based on the available evidence. If this optimal recommendation cannot be followed due to practical restrictions, e.g. therapeutic drug monitoring or a lower dose is not available, then the health care professional should consider the next best option.

Brief summary and justification of choices:
Phenprocoumon reduces blood coagulation by inhibition of VKORC1 enzyme activity. VKORC1 gene variants may lead to reduced production of the VKORC1 protein. Lower phenprocoumon doses are then needed to achieve the desired INR.
AA increases the risk of developing INR > 6, i.e. periods with high bleeding risk, and decreases the maintenance dose. Contrary to acenocoumarol, there is no evidence that a lower initial phenprocoumon dose reduces the percentage of patients with INR > 6 on day 4, but the maintenance dose does decrease by the same extent for both coumarins. One study showed no significant difference in clinical effect for all genotypes combined when using a pharmacogenetic dosing algorithm for the first 5-7 days. However, a later study showed the pharmacogenetic dosing algorithm to increase the percentage of time with a therapeutic INR and decrease the percentage of time with a supratherapeutic INR (> 3.0) for patients younger than 75 years with two or more VKORC1 and/or CYP2C9 variants. However, for patients of 75 years and older, the pharmacogenetic dosing algorithm decreased the percentage of time with a therapeutic INR and increased the percentage of time with a supratherapeutic INR (> 3.0) (significantly for the whole group and numerically for patients with two or more VKORC1 and/or CYP2C9 variants for whom significance could not be determined due to the presence of only one such patient in the control group). This might be due to the algorithm being suboptimal for patients of 75 years and older. Based on the observed clinical effects for AA, the KNMP Pharmacogenetics Working Group decided that a recommendation to reduce the initial dose is required for this gene-drug interaction (yes/yes-interaction).
GA appears to have a more pronounced effect on the bleeding risk than the maintenance dose, though data on an increased bleeding risk were not confirmed in other studies. Moreover, GA is the most common genotype among European Caucasians, and the standard dose will therefore be largely based on this genotype. So it does not seem meaningful to recommend additional monitoring. This is why a decision was made that this concerns a gene-drug interaction but that no action is required (yes/no-interaction).
You can find a detailed overview of the observed clinical and kinetic effects per genotype in the background information text of the gene-drug interactions on the KNMP Kennisbank. You might also have access to this background information text via your pharmacy or physician electronic decision support system.
More detailed substantiation of the choice per genotype is given below.

AA: Brehm 2016, Brehm 2013, and Reitsma 2005 did not find a significantly increased risk of major bleeding, although Reitsma did find an increased risk for GA+AA and Brehm 2013 found a trend. Schalekamp 2007 and the extension to this study, Verhoef 2012 found an increased risk of INR > 6 (significant overanticoagulation). Reitsma 2005, Schalekamp 2007 and Verhoef 2012 are all studies performed in the Netherlands where patients were started on anticoagulant therapy and subsequently monitored by the National INR Monitoring Service (Thrombosis Service).
As the initial dose used by most sites of the Thrombosis Service differs for patients < 70 years (either 9-3-1.5 or 6-3-1.5 mg) and for patients ≥ 70 years or with relative contraindication(s) (either 12-6-3 or 9-6-3 mg), a decision was made to recommend a percentage decrease in the initial dose equivalent to the decrease in the maintenance dose for AA. The weighted mean of the calculated decrease in maintenance dose for AA is a decrease to 51% of the maintenance dose for GG (median 50%; ranging per study from 46-58%). This was translated to an initial dose of 50% to be more achievable in clinical practice. A decision was also made to

recommend additional monitoring at hospitals, where patients are initiated on anticoagulant therapy by residents or internists.

GA: Reitsma 2005 found an increased risk of major bleeding, but Brehm 2016 and Brehm 2015 did not. Schalekamp 2007 and the extension to this study, Verhoef 2012 found no increased risk of INR > 6 (significant over-anticoagulation).

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

The Dutch Pharmacogenetics Working Group considers genotyping before starting phenprocoumon to be to be beneficial for drug safety. It is advised to genotype these patients before (or directly after) drug therapy has been initiated to guide drug and dose selection.

The clinical implication of the gene-drug interaction scores 3 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):

Despite very careful dose titration by the Dutch Thrombosis Service, the percentage of patients developing INR ≥ 6 (severity code D corresponding to CTCAE grade 3) was enhanced for patients homozygous for the variant VKORC1 allele (VKORC1 -1639 AA) compared to patients homozygous for the wild type allele (VKORC1 -1639 GG). 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).

Two studies confirmed VKORC1 -1639 AA to result in a severe clinical effect (score of D corresponding to CTCAE grade 3). However, 39% of the patients in the largest of these studies (Verhoef 2012) were derived from the smallest of these studies (Schalekamp 2007). So, a severe clinical effect of AA was only shown in one independent study.

Reitsma 2005 reported an increase in major bleeding in VKORC1 -1639 GA, but the increase did not reach significance in VKORC1 -1639 AA. Because the result of Verhoef 2012 was partly based on the patients in Schalekamp 2007 and because the result in Reitsma 2005 only reached significance for GA but not for AA, both studies were considered to contribute only for 50% to the evidence. So, the total amount of studies confirming a severe clinical effect for VKORC1 -1639 AA was 2 (one study contributing fully and two studies contributing 50%). This results in 2 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 ≥ 3 (2 points for two publications with level of evidence score ≥ 3).

The number needed to genotype should be deduced from the increase in the percentage of patients with bleeding for VKORC1 -1639 AA. INR > 6 only has a severity code D (CTCAE grade 3), because an increase in INR > 6 corresponds to an increase in bleeding. However, the incidence of bleeding is much lower than the incidence of INR > 6 and patients do not notice INR > 6 if it does not result in bleeding. For this reason, INR > 6 is not suitable for calculation of the number needed to genotype to prevent a serious adverse event. However, there are no studies investigating bleeding that can be employed for calculation of the number needed to genotype. Reitsma 2005 investigated major bleeding, but only mentioned odds ratios, not the incidence of major bleeding in VKORC1 -1639 GG or in the general population. Brehm 2013 and Brehm 2016 investigated bleeding in patients with a ventricular assist device, which is not the major patient group treated with phenprocoumon. In addition, this study is performed in Germany, so without involvement of the Dutch Thrombosis Service. Because data to calculate the number needed to genotype are lacking, no points can be assigned for the number needed to genotype. Because major bleeding is a rare event in patients treated with phenprocoumon, it is not very likely that points could have been assigned (number needed to genotype ≤ 1000) if data to calculate the number needed to genotype would have been available. Reitsma 2005 found an OR of 2.6 for major bleeding for VKORC1 -1639 AA compared to VKORC1 -1639 GG and Verhoef 2012 reported 17% of patients to have the AA genotype. Because at low event frequencies, the OR is approximately equal to the relative risk, the difference in risk between AA and GG would be 1.6 times the risk in GG. With 5.88 patients to be genotyped to find one VKORC1 -1639 AA, a number needed to genotype ≤ 1000 would require the percentage of VKORC1 -1639 GG with major bleedings to be higher than 0.37%. Because the number needed to genotype could not be calculated and is likely to be higher than 1000, this results in 0 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 ≥ 3 (only points for NNG ≤ 1000).

The Summary of Product Characteristics (SmPC) of phenprocoumon does not mention any VKORC1 phenotype or genotype. This results in 0 out of the maximum of 2 points for the fourth and last criterion of the clinical implication score, the pharmacogenetics information in the SmPC (only points for at least one genotype/phenotype mentioned in the SmPC).

The table below follows the KNMP nomenclature for the VKORC1 polymorphism and genotypes. The nomenclature used in the table below may therefore differ from the nomenclature used by the authors in the article.

Source	Code	Effect	Comments
ref. 1 Zhang Y et al. Age-stratified outcome of a genotype-	3	Data from the 159 patients in Verhoef 2013 who had at least 10 weeks follow-up were reanalysed. Of these patients, 79 received genotype-guided treatment (55 patients < 75 years of age and 24 patients ≥ 75 years of age) and 80 received con-	Author's conclusion: "The results support the use of

<table>
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<td>guided dosing algorithm for acenocoumarol and phenprocoumon.
J Thromb Haemost 2017;15:454-464.
PubMed PMID: 27992949.

ref. 1, continuation</td>
<td>genotype-guided versus not genotype-guided therapy, patients < 75 years: AA#</td>
<td>trol treatment (63 patients < 75 years of age and 17 patients ≥ 75 years of age). After exclusion of patients due to protocol violations, 49 patients remained in the genotype-guided group (33 patients < 75 years of age and 16 patients ≥ 75 years of age) and 58 in the control group (47 patients < 75 years of age and 11 patients ≥ 75 years of age).
All INRs were measured during the first 12 weeks of treatment.
Patient characteristics in the different groups were similar, except for patients < 75 year having a higher weight in the genotype-guided group compared to the control group (mean respectively 92 kg and 85 kg).
Approximately half of the patients used relevant co-medication (drugs with a potentiating effect). None of the patients used amiodarone, which was included in the algorithms.
Differences in percentages of time in or outside the therapeutic range were adjusted for height, weight, sex, enzyme inhibitors, and enzyme inducers.

Genotyping:
- 55x GG
- 72x GA
- 31x AA
- 1x genotype unknown (clinical algorithm, < 75 years)

Results:
<table>
<tr><td colspan="4">Genotype-based algorithm versus clinical algorithm:</td></tr>
<tr><td></td><td></td><td></td><td>value for the clinical algorithm</td></tr>
<tr><td rowspan="11">% of time in the therapeutic range</td><td>< 75 years, no CYP2C9 and VKORC1 variants</td><td>NS</td><td>53.9%</td></tr>
<tr><td>< 75 years, one CYP2C9 or VKORC1 variant</td><td>NS</td><td>63.0%</td></tr>
<tr><td>< 75 years, two or more CYP2C9 and/or VKORC1 variants</td><td>+ 14.0% (S)</td><td>52.1%</td></tr>
<tr><td>≥ 75 years, no CYP2C9 and VKORC1 variants</td><td>NS</td><td>56.0%</td></tr>
<tr><td>≥ 75 years, one CYP2C9 or VKORC1 variant</td><td>NS</td><td>67.2%</td></tr>
<tr><td>≥ 75 years, two or more CYP2C9 and/or VKORC1 variants</td><td>significance could not be determined (n = 1 in the control group)</td><td>55.6%</td></tr>
<tr><td>< 75 years</td><td>+ 9.5% (S)</td><td>55.7%</td></tr>
<tr><td>≥ 75 years</td><td>- 17.9% (S)</td><td>63.3%</td></tr>
<tr><td colspan="3">A per-protocol analysis showed similar results, but the differences did not reach significance in this analysis (p = 0.08 for < 75 years and p = 0.05 for ≥ 75 years).</td></tr>
<tr><td>% of time with a suprathe-</td><td>< 75 years, no CYP2C9 and VKORC1 variants</td><td>NS</td><td>16.1%</td></tr>
</table>
</td>
<td>genotype-guided dosing for phenprocoumon in patients < 75 years. For patients ≥ 75 years the phenprocoumon algorithm should be revised and further tested.”</td>
</tr>
</table>

ref. 1, continuation		rapeutic INR (> 3.0)	< 75 years, one CYP2C9 or VKORC1 variant	NS	18.8%	
			< 75 years, two or more CYP2C9 and/or VKORC1 variants	- 21.7% (S)	40.0%	
			≥ 75 years, no CYP2C9 and VKORC1 variants	NS	13.2%	
			≥ 75 years, one CYP2C9 or VKORC1 variant	+ 21.3% (S)	5.5%	
			≥ 75 years, two or more CYP2C9 and/or VKORC1 variants	significance could not be determined (n = 1 in the control group)	40.8%	
			< 75 years	- 9.6% (S)	27.1%	
			≥ 75 years	+ 27.5% (S)	9.9%	
			A per-protocol analysis showed similar results, but the difference was not significant for < 75 years.			
		% of time with a subthera-peutic INR (< 2.0)	< 75 years, no CYP2C9 and VKORC1 variants	NS	30.0%	
			< 75 years, one CYP2C9 or VKORC1 variant	NS	18.3%	
			< 75 years, two or more CYP2C9 and/or VKORC1 variants	+ 7.7% (S)	8.0%	
			≥ 75 years, no CYP2C9 and VKORC1 variants	NS	30.8%	
			≥ 75 years, one CYP2C9 or VKORC1 variant	NS	27.3%	
			≥ 75 years, two or more CYP2C9 and/or VKORC1 variants	significance could not be determined (n = 1 in the control group)	3.5%	
			< 75 years	NS	17.2%	
			≥ 75 years	NS	26.9%	
			A per-protocol analysis showed similar results.			
		calculated dose for the pa-tients in the geno-type-gui-ded group (in mg/day)	< 75 years, no CYP2C9 and VKORC1 variants	+ 0.60 (S)	2.4	
			< 75 years, one CYP2C9 or VKORC1 variant	NS	2.2	
			< 75 years, two or more CYP2C9 and/or VKORC1 variants	- 0.70 (S)	2.3	
			≥ 75 years, no	+ 0.60 (S)	1.8	
	geno-type-guided versus not ge-notype-guided therapy, pa-tients ≥ 75 years: A					

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<td>ref. 1, continuation</td>
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<table>
<tr><td></td><td>CYP2C9 and VKORC1 variants</td><td></td><td></td></tr>
<tr><td></td><td>≥ 75 years, one CYP2C9 or VKORC1 variant</td><td>NS</td><td>1.9</td></tr>
<tr><td></td><td>≥ 75 years, two or more CYP2C9 and/or VKORC1 variants</td><td>- 0.40 (S)</td><td>1.7</td></tr>
<tr><td></td><td>< 75 years</td><td>- 0.20 (S)</td><td>2.3</td></tr>
<tr><td></td><td>≥ 75 years</td><td>NS</td><td>1.8</td></tr>
<tr><td>calculated dose for the patients in the control group (in mg/day)</td><td>< 75 years, no CYP2C9 and VKORC1 variants</td><td>+ 0.7 (S)</td><td>2.9</td></tr>
<tr><td></td><td>< 75 years, one CYP2C9 or VKORC1 variant</td><td>NS</td><td>2.3</td></tr>
<tr><td></td><td>< 75 years, two or more CYP2C9 and/or VKORC1 variants</td><td>+ 0.6 (S)</td><td>1.6</td></tr>
<tr><td></td><td>≥ 75 years, no CYP2C9 and VKORC1 variants</td><td>- 0.6 (S)</td><td>2.2</td></tr>
<tr><td></td><td>≥ 75 years, one CYP2C9 or VKORC1 variant</td><td>NS</td><td>1.8</td></tr>
<tr><td></td><td>≥ 75 years, two or more CYP2C9 and/or VKORC1 variants</td><td>not determined</td><td></td></tr>
<tr><td></td><td>< 75 years</td><td>NS</td><td>2.2</td></tr>
<tr><td></td><td>≥ 75 years</td><td>trend for a decrease (p = 0.10) (NS)</td><td>1.9</td></tr>
</table>
Note: The authors indicate that the increased time above the therapeutic INR might not represent an interaction with genotype, but an insufficient age-related dose correction in the genotype-guided algorithm.
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<td>ref. 2
Brehm K et al. Genetic variations of phenprocoumon metabolism in patients with ventricular assist devices. Eur J Cardiothorac Surg 2016;50:275-80. PubMed PMID: 26984978.</td>
<td>3</td>
<td>63 patients with ventricular assist device support, treated with phenprocoumon for a period of 0.85-65.02 months (mean 10.75 months), were retrospectively studied. Phenprocoumon therapy was started in the intensive care unit after the patient reached a stable condition and oral food intake was possible. Standard anticoagulation protocol included phenprocoumon therapy with a target INR of 2-3 plus acetylsalicylic acid 100 mg/day. However, the target INR for the majority of patients was 2-2.5 and acetylsalicylic acid was discontinued after the occurrence of recurrent bleeding events. Approximately half of the patients receiving a ventricular assist device in the same period were deceased and not included.
Major bleeding was defined as bleeding requiring imminent medical therapy and minor bleeding as bleeding not requiring medical treatment (epistaxis, bleeding after dental procedures and mucosal bleeding). There were 31 episodes of major bleeding in 19 patients. Multiple minor bleedings were reported in 35 patients.
There were 17 thromboembolic events in 11 patients: 4 thromboses of the pump necessitating change of the device, 4 ischaemic strokes, 6 transient ischaemic episodes, 1 splenic</td>
<td>Author’s conclusion:
”VKORC polymorphism affects phenprocoumon dosage in the initiation as well as the maintenance phase. High rates of bleeding complications and thromboembolic events were found at the beginning of phenprocoumon therapy in ventricular assist device patients. Therefore, a genotype-guided dosage algorithm</td>
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<tr>
<td>ref. 2, continuation</td>
<td>AA: A
GA: A</td>
<td>infarction, 1 central retinal artery occlusion and 1 pulmonary embolism.
High complication (major bleeding or thromboembolism) rates were observed particularly in the early post-operative period.
Relevant co-medication was not excluded.
The influence of genotypes on the occurrence of adverse events was evaluated by univariate logistic regression analysis.

Genotyping:
- 26x GG
- 20x GA
- 17x AA

Results:
<table>
<tr><td colspan="4">Results compared to GG:</td></tr>
<tr><td></td><td>AA</td><td>GA</td><td>value for GG</td></tr>
<tr><td>bleeding events</td><td>NS</td><td>NS</td><td></td></tr>
<tr><td>thromboembolic events</td><td>NS</td><td>NS</td><td></td></tr>
<tr><td>dose corrected INR increase during the loading phase</td><td>x 2.3 (S)</td><td>x 2.3 (S)</td><td>0.04</td></tr>
<tr><td>phenprocoumon maintenance dose (in mg/week)</td><td>x 0.58 (S)</td><td>x 0.66 (S)</td><td>15.7</td></tr>
</table>
</td>
<td>might be useful in ventricular assist device patients.”

Maintenance dose versus GG:
GA: 66%
AA: 58%</td>
</tr>
<tr>
<td>ref. 3
Botton et al.
A new algorithm for weekly phenprocoumon dose variation in a southern Brazilian population: role for CYP2C9, CYP-3A4/5 and VKORC1 genes polymorphisms.
Basic Clin Pharmacol Toxicol 2014;114:323-9.
PubMed PMID: 24224579.</td>
<td>3

GA: A
AA: A</td>
<td>198 patients with various INR targets on maintenance therapy with phenprocoumon. Relevant co-medication was not excluded.

Genotyping:
- 73x GG
- 100x GA
- 25x AA

Maintenance dose versus GG:
- GA: decrease by 24% (from 18.63 mg to 14.18 mg) (S)
- AA: decrease by 43% (from 18.63 mg to 10.67 mg) (S)</td>
<td>Authors’ conclusion:
‘Polymorphisms 1639G>A and 1173C>T in VKORC1 are associated with lower doses.’

Maintenance dose versus GG:
GA: 76%
AA: 57%</td>
</tr>
<tr>
<td>ref. 4
Verhoef TI et al.
A randomized trial of genotype-guided dosing of acenocoumarol and phenprocoumon.
N Engl J Med 2013;369:2304-12.
PMID:24251360.</td>
<td>3

genotype-guided versus</td>
<td>Patients without prior exposure to coumarin therapy were treated with phenprocoumon for 12 weeks. The dose administered during the first 5-7 days was guided by an algorithm that included CYP2C9 and VKORC1 genotypes (n=83) or guided by an algorithm based on clinical information only (n=81). The INR target was 2.0-3.0. Relevant co-medication was not excluded. There were no amiodarone users. Patients with venous thromboembolism (17%) were commonly given low-molecular-weight heparin until achieving therapeutic INR.

Genotypering:
- 57x GG
- 73x GA
- 34x AA

Genotype-based algorithm versus clinical algorithm:
- The time that the INR was in the therapeutic range throughout the treatment did not increase (NS)
- There was a trend towards an increase in the time that the INR was in the therapeutic range in the first four weeks; the trend was an increase by 19% (from 41.2% to 49.0%; p =</td>
<td>Authors’ conclusion:
‘Genotype-guided dosing of acenocoumarol or phenprocoumon did not improve the percentage of time in the therapeutic range during the 12 weeks after the initiation of therapy.’</td>
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</table>

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<tr>
<td>ref. 4, continuation

Baranova EV et al. Dosing algorithms for vitamin K antagonists across VKORC1 and CYP-2C9 genotypes. J Thromb Haemost 2017;15:465-472. PubMed PMID: 28063245.</td>
<td>not genotype-guided therapy : AA</td>
<td>0.05)
- No difference in the incidence of adverse events and thromboembolism (NS)
- No difference in the percentage of patients with an INR ≥ 4, the percentage of time with an INR was ≥ 4 or < 2, the time until achieving an INR in the therapeutic range and the time until achieving a stable dose (NS)

When the acenocoumarol and phenprocoumon data were pooled, the time that the INR was in the therapeutic range in the first four weeks of treatment was higher for the genotype-based algorithm than for the clinical algorithm (52.8% and 47.5% of the time respectively) (S). There were no differences in weeks 5-8 and weeks 9-12. However, the results of Baranova 2017 suggested the higher percentage of time in therapeutic range in the first 4 weeks to be due to the patients without a CYP2C9 and or VKORC1 variant:
<table>
<tr><td colspan="4">Genotype-based algorithm versus clinical algorithm:</td></tr>
<tr><td></td><td>genotype group</td><td>first 4 weeks</td><td>first 12 weeks</td></tr>
<tr><td>% of time in the therapeutic range</td><td>no CYP2C9 and VKORC1 variants</td><td>+ 14.68% (S, but only a trend after Bonferroni correction (significance for p < 0.001) (NS, p = 0.002))</td><td>trend for an increase, p = 0.087 (NS)</td></tr>
<tr><td></td><td>one or more CYP2C9 variants and no VKORC1 variant</td><td>NS</td><td>NS</td></tr>
<tr><td></td><td>no CYP2C9 variants and one VKORC1 variant</td><td>NS</td><td>NS</td></tr>
<tr><td></td><td>one or more CYP2C9 variants and one VKORC1 variant</td><td>NS</td><td>NS</td></tr>
<tr><td></td><td>no CYP2C9 variants and two VKORC1 variants</td><td>NS</td><td>NS</td></tr>
<tr><td></td><td>one or more CYP2C9 variants and two VKORC1 variants</td><td>NS</td><td>NS</td></tr>
<tr><td>% of time with a supra-therapeutic INR (> 3.0)</td><td>no CYP2C9 and VKORC1 variants</td><td>NS</td><td>NS</td></tr>
<tr><td></td><td>one or more CYP2C9 variants and no VKORC1 variant</td><td>NS</td><td>NS</td></tr>
<tr><td></td><td>no CYP2C9 variants and</td><td>NS</td><td>NS</td></tr>
</table>
</td>
<td>Authors' conclusion:
'Four weeks after therapy initiation, genotype-guided dosing increased the mean percentage of time in the therapeutic INR range in the VKORC1 GG–CYP2C9*1*1 subgroup as compared with the non-genetic dosing (difference of 14.68%). For the VKORC1 AA–CYP2C9*1*1 subgroup, there was a higher risk of under-anticoagulation with the genotype-guided algorithm (difference of 19.9%). Twelve weeks after therapy initiation, no statistically significant differences in anticoagulation control between trial arms were noted across the VKORC1–CYP-2C9 genetic subgroups.
EU-PACT genetic-guided dose initiation algorithms for acenocoumarol and phenprocoumon could have predicted the dose overcautiously in the VKORC1 AA–CYP2C9*1*1 subgroup. Adjustment of the genotype-guided algorithm</td>
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ref. 4, continuation				one VKORC1 variant		could lead to a higher benefit of genotyping.'
				one or more CYP2C9 variants and one VKORC1 variant	trend for a decrease, p = 0.098 (NS)	NS
				no CYP2C9 variants and two VKORC1 variants	trend for a decrease, p = 0.087 (NS)	trend for a decrease, p = 0.057 (NS)
				one or more CYP2C9 variants and two VKORC1 variants	- 20.50% (S, but NS after Bonferroni correction)	NS
			% of time with a sub-therapeutic INR (< 2.0)	no CYP2C9 and VKORC1 variants	- 20.29% (S, before and after Bonferroni correction)	trend for a decrease, p = 0.083 (NS)
				one or more CYP2C9 variants and no VKORC1 variant	NS	NS
				no CYP2C9 variants and one VKORC1 variant	NS	trend for an increase, p = 0.081 (NS)
				one or more CYP2C9 variants and one VKORC1 variant	NS	NS
				no CYP2C9 variants and two VKORC1 variants	+ 19.89% (S, before and after Bonferroni correction)	+ 12.99% (S, but NS after Bonferroni correction)
				one or more CYP2C9 variants and two VKORC1 variants	trend for an increase, p = 0.075 (NS)	NS
			Results were similar after sensitivity analysis for both coumarins separately and in the per-protocol dataset.			
ref. 5 Abduljalil K et al. Quantifying the effect of covariates on concentrations and effects of steady-state phenprocoumon using a population pharmacokinetic/pharmacodynamic model. Clin Pharmacokinet 2013;52:359-71. PMID: 23519598.	3 GA: A AA: A	278 patients with various INR targets on maintenance therapy with phenprocoumon. Relevant co-medication was not excluded. A pharmacokinetic/ pharmacodynamic model showed significant effects of CYP3A inhibitors/inducers, but no significant effects of CYP2C9 inhibitors/inducers on clearance. Genotyping: - 97x GG - 130x GA - 51x AA Maintenance dose versus GG: - GA: decrease by 20% (from 16.66 mg to 13.36 mg per week) (S) - AA: decrease by 49% (from 16.66 mg to 8.56 mg per week) (S)			Authors' conclusion: 'The model confirmed CYP2C9 and VKORC1 variants as the major predictors of variability in phenprocoumon concentrations and effects, together with body weight, age, comedication with CYP3A modifiers (i.e. inhibitors or inducers) and

ref. 5, continuation		A pharmacokinetic/pharmacodynamic model showed significant effects of the VKORC1 variant on sensitivity to phenprocoumon. NOTE: Genotyping was for the polymorphism 1173C>T.	presence of atrial fibrillation.' **Maintenance dose versus GG:** GA: 80% AA: 51%
ref. 6 Brehm K et al. Mechanical heart valve recipients: anticoagulation in patients with genetic variations of phenprocoumon metabolism. Eur J Cardiothorac Surg 2013;44:309-14. PMID:23423913.	3 GA: C AA: A	178 patients with a mechanical heart valve prosthesis received phenprocoumon for on average 6.7 years. The INR target was 2.5-3.5. Relevant co-medication was not excluded. Genotyping: - 62x GG - 91x GA - 25x AA GA versus GG: - No difference in the risk of minor bleeding (NS) - No difference in the risk of major bleeding (NS) - Increased risk of INR > 5 with OR = 5.4 (95% CI: 1.2-24.1) (S) - No difference in the risk of venous thromboembolism (NS) - The maintenance dose decreased by 17% (from 19.0 to 15.8 mg/week) (NS) AA versus GG: - No difference in the risk of minor bleeding (NS) - No significant difference in the risk of major bleeding, but there was a trend towards an increased risk (from 13% to 27% of the patients; OR = 2.5; 95% CI: 0.77-10; p = 0.1) - No difference in the risk of INR > 5 (NS) - No difference in the risk of venous thromboembolism (NS) - The maintenance dose decreased by 54% (from 19.0 to 8.7 mg/week) (S)	Authors' conclusion: 'VKORC polymorphism affects phenprocoumon dosage and anticoagulation-related complication rates in mechanical heart valve recipients. Genotyping may help to identify patients at particular risk of anticoagulation-related complications.' **Maintenance dose versus GG:** GA: 83% AA: 46%
ref. 7 Verhoef TI et al. Long-term anticoagulant effects of CYP2C9 and VKORC1 genotypes in phenprocoumon users. J Thromb Haemost. 2012;10:2610-2. PMID: 23016521.	3 GA: AA[#] GA: A AA: AA[#]	Data from 747 phenprocoumon users from two different studies were analysed. 39% of the patients participated in the Schalekamp 2007 study, which is also included separately in this risk analysis. This was the only study that generated data only on the first 6 months of treatment. Data up to 18 months were derived from another study. The INR target was 2.0-3.5 for all patients. Relevant co-medication was not excluded. Genotyping: - 280x GG - 341x GA - 126x AA GA versus GG (first month): - Factor 0.85 decrease in the percentage of patients with at least one subtherapeutic INR (from 89% to 76%) (S) - Factor 1.5 increase in the percentage of patients with at least one supratherapeutic INR (from 33% to 48%) (S) - No difference in the percentage of patients with at least one INR > 6 (NS) No differences between GA and GG were found after the first month of treatment. AA versus GG (first month): - Factor 0.56 decrease in the percentage of patients with at least one subtherapeutic INR (from 89% to 50%) (S) - Factor 2 increase in the percentage of patients with at least one supratherapeutic INR (from 33% to 66%) (S)	Authors' conclusion: 'The results of this study suggest that pharmacogenetic information might help to prevent subtherapeutic or supratherapeutic INRs in the first month of phenprocoumon therapy and thereby reduce the risk of adverse events. The value of this information after the first month of phenprocoumon treatment appears to be limited.'

ref. 7, continuation	AA: D	- Factor 5.7 increase in the percentage of patients with at least one INR > 6 (from 3% to 17%) (S) No differences between AA and GG were found after the first month of treatment. NOTE: Genotyping was for the polymorphism 1173C>T.	
ref. 8 Geisen C et al. Prediction of phenprocoumon maintenance dose and phenprocoumon plasma concentration by genetic and non-genetic parameters. Eur J Clin Pharmacol 2011;67:371-81.	4 GA: A AA: A	75 patients (30x GG, 33x GA, 12x AA) on maintenance therapy with phenprocoumon. The INR target was 2.0-3.0. Relevant co-medication was taken by 59% of the patients, but co-medication did not have a significant effect on the maintenance dose. Median maintenance dose versus GG: - GA: decrease by 31% (from 2.79 mg to 1.93 mg/day) (S for the trend) - AA: decrease by 50% (from 2.79 mg to 1.40 mg/day) (S for the trend) VKORC1 genotype is an independent variable for the maintenance dose (multivariable regression analysis) and also the variable with the most effect. VKORC1 genotype accounts for 38% of the variability in the maintenance dose.	Authors' conclusion: "The largest dose differences were observed among VKORC1 genotypes." **Median maintenance dose versus GG:** GA: 69% (S) AA: 50% (S)
ref. 9 Teichert M et al. Dependency of phenprocoumon dosage on polymorphisms in the VKORC1, CYP2C9, and CYP4F2 genes. Pharmacogenet Genomics 2011;21:26-34.	3 GA: A AA: A	244 patients (90x GG, 101x GA, 53x AA) on maintenance therapy with phenprocoumon. Relevant co-medication was not excluded. The median maintenance dose for GG was 17.2 mg/week. Dose differences were corrected for INR targets (among other factors). Maintenance dose versus GG: - GA: decrease by 4.51 mg/week (S) - AA: decrease by 9.62 mg/week (S) VKORC1 genotype explained 26% of the variation in the maintenance dose. NOTE: Genotyping was for the polymorphism rs10871454 that is fully linked to the VKORC1 1639G>A polymorphism. It is therefore referred to as the A-allele in this summary.	Authors' conclusion: "Phenprocoumon maintenance dosage depended on polymorphisms in the VKORC1 gene." **Median maintenance dose versus GG:** GA: 74% (S) AA: 48% (S)
ref. 10 Luxembourg B et al. Impact of pharmacokinetic (CYP2C9) and pharmacodynamic (VKORC1, F7, GGCX, CALU, EPHX1) gene variants on the initiation and maintenance phases of phenprocoumon therapy. Thromb Haemost 2011;105:169-80.	3 GA: A GA: AA[#]	54 patients (25x GG, 20x GA, 9x AA) who started phenprocoumon therapy and 91 patients (36x GG, 39x GA, 16x AA) on phenprocoumon maintenance therapy. The INR target was 2.0-3.0. The median initial dose was 18 mg divided over 3 days. No dosing algorithm was used. Relevant co-medication was not excluded. Median measurements are given. *Initiation phase:* GA versus GG: - Difference in dose on day 4 (S for the trend GG, GA, AA) - The cumulative dose on day 5 decreased by 15% from 30.0 to 25.5 mg (S for the trend) - The first INR measured increased by 0.33 from 1.18 to 1.51 (S for the trend) - The time to stable INR decreased by 61% from 31 to 12 days (S for the trend). The HR for achieving stable INR sooner than GG and AA was 3.06 (95% CI: 1.68-5.58). - The time to first INR > 3.0 decreased by 53% from 17 to 8 days (S for the trend) - Decreased risk of INR > 3.0 (OR = 0.23; 95% CI: 0.05-0.96) - No difference in the percentage of time that INR > 3.0 (both 0%)	Authors' conclusion: "Compared to the VKORC1 genotype, early INR values were less informative in the prediction of outcome parameters such as time to stable INR and time above the INR range."

ref. 10, continuation	AA: AA[#] AA: B	AA versus GG: - Difference in dose on day 4 (S for the trend GG, GA, AA) - The cumulative dose on day 5 decreased by 25% from 30.0 to 22.5 mg (S for the trend) - The first INR measured increased by 0.55 from 1.18 to 1.73 (S for the trend) - The time to stable INR decreased by 23% from 31 to 24 days (S for the trend) - The time to first INR > 3.0 decreased by 65% from 17 to 6 days (S for the trend) The HR for achieving INR > 3.0 sooner than GG was 28.04 (95% CI: 4.3-183.43). - Increased risk of INR > 3.0 (OR = 4.46 (NS (significance not calculated), S versus GA)). - The percentage of time that INR > 3.0 increased from 0% to 35.3% (S) - 44% of the AA patients had an INR > 4 during the initiation phase General: - Multiple linear regression analysis showed that the VKORC1 genotype was an independent predictor of the time that INR was > 3.0 in the initiation phase *Maintenance therapy:* - No significant effects of VKORC1 genotype on time that INR was < 2.0 or > 3.0 The VKORC1 genotype had a higher predictive power for the time to stable INR and time above the INR range in the initiation phase than the first INR measurement.	
ref. 11 Nowak-Göttl U et al. In pediatric patients, age has more impact on dosing of vitamin K antagonists than VKORC1 or CYP2C9 genotypes. Blood 2010;116:6101-5.	3 GA: AA AA: A	59 children (27x GG, 25x GA, 7x AA) received phenprocoumon therapy (n=26) or warfarin (n=34). Relevant co-medication was not excluded. Maintenance dose versus GG: - GA: no significant difference (NS) - AA: significant decrease (S) Age is the most critical variable in determining the phenprocoumon dose in children (explains 25.5% of the variation); the model did not improve significantly on inclusion of the VKORC1 genotype as a variable.	Authors' conclusion: "In children, the most critical factor in determining VKA dose is age. VKORC1/CYP2C9 genotypes only marginally explain dose variations."
ref. 12 Puehringer H et al. VKORC1 -1639G>A and CYP2C9*3 are the major genetic predictors of phenprocoumon dose requirement. Eur J Clin Pharmacol 2010;66:591-8.	3 GA: A AA: A	185 patients (65x GG, 87x GA, 29x AA) on maintenance therapy with phenprocoumon. The INR target was 2.0-3.0. Relevant co-medication was not excluded. Maintenance dose versus GG: - GA: decrease by 19% (from 15.5 mg to 12.5 mg/week) (S for the trend) - AA: decrease by 43% (from 15.5 mg to 8.8 mg/week) (S for the trend) VKORC1 genotype is an independent and also the most critical variable in determining the maintenance dose (multivariable regression analysis) and explains 14.2% of the variability in the maintenance dose.	Authors' conclusion: "The VKORC1 −1639G>A polymorphism had the highest impact on the maintenance dose of phenprocoumon." **Maintenance dose versus GG:** GA: 81% (S) AA: 57% (S)
ref. 13 Cadamuro J et al. Genetic determinants of acenocoumarol and phenpro-	3	126 patients (35x GG, 64x GA, 27x AA) on maintenance therapy with phenprocoumon. Relevant co-medication was taken by 44% of the patients.	Authors' conclusion: "These results reveal that interindividual variability

coumon maintenance dose requirements. Eur J Clin Pharmacol 2010;66:253-60. **ref. 13, continuation**	GA: A AA: A	Maintenance dose (corrected for age, sex and last INR) versus GG: - GA: decrease by 21% (from 19.08 mg to 15.12 mg/week) (S for the trend) - AA: decrease by 51% (from 19.08 mg to 9.27 mg/week) (S for the trend) VKORC1 genotype is an independent variable for the maintenance dose (multivariable regression analysis). Age, sex, last INR and VKORC1 and CYP2C9 genotypes combined account for 55% of the variability in the maintenance dose. NOTE: Genotyping was for the polymorphism 1173C>T.	in weekly acenocoumarol maintenance dose requirement is mainly dependent on the VKORC1 1173 C>T and the CYP-2C9*3 alleles." **Maintenance dose versus GG:** GA: 79% (S) AA: 49% (S)
ref. 14 Arnold ML et al. Pharmacogenetic testing for guiding de novo phenprocoumon therapy in stroke patients. Cerebrovasc Dis 2009;28:468-71.	4 GA: AA[#] GA: A AA: AA[#] AA: A	47 patients with a TIA or stroke (15x GG, 27x GA, 5x AA) were started on phenprocoumon at the hospital. The INR target was 2.0-3.0. Relevant co-medication was not excluded, but co-medication did not have a significant effect on the response to phenprocoumon. GA versus GG: - The time to therapeutic INR decreased by 32% from 6.5 to 4.4 days (S for the trend) - Significant difference in cumulative dose until reaching therapeutic INR (S for the trend) AA versus GG: - The time to therapeutic INR decreased by 51% from 6.5 to 3.2 days (S for the trend) - Significant difference in cumulative dose until reaching therapeutic INR (S for the trend) 80% of the patients were discharged from hospital immediately after achieving therapeutic INR. NOTE: Genotyping was for the *2-allele (polymorphism 2255C>T). According to Spreafico et al. (Pharmacogenomics 2008;9:1237-50) the *2-allele (rs2359612, VKORC1 2255 C>T) is equivalent to hereditary class A and therefore to the -1639A allele. It is therefore referred to as the A-allele in this summary.	Authors' conclusion: "In patients with cerebrovascular disease, genotyping for VKORC1 alone can strongly predict the individual response to de novo phenprocoumon treatment. The size of the pharmacogenetic test's potential effect on a more efficient use of hospital capacities remains to be shown by a controlled interventional study."
ref. 15 Qazim B et al. Dependency of phenprocoumon dosage on polymorphisms in the VKORC1 and CYP-2C9 genes. J Thromb Thrombolysis 2009;28:211-4.	3 GA: AA AA: AA	53 patients (19x GG, 23x GA, 11x AA) on maintenance therapy with phenprocoumon for various indications. Co-medication that potentiated (n = 45) or weakened (n = 12) the effect of phenprocoumon was present. Significances of the dose differences were not given. GA versus GG: - No difference in INRs - The maintenance dose decreased by 29% from 15.3 to 10.9 mg/week (NS) AA versus GG: - No difference in INRs - The maintenance dose decreased by 49% from 15.3 to 7.8 mg/week (NS) NOTE: According to Puehringer et al., 2010, the polymorphism VKORC1 3730G>A that was also investigated was not independent of -1639G>A and was therefore not included in the summary.	Authors' conclusion: "Though VKORC1 and CYP2C9 polymorphisms influence the phenprocoumon dosage necessary to achieve therapeutic anticoagulation, anticoagulation is therapeutic if carefully monitored." **Maintenance dose versus GG:** GA: 71% (S) AA: 51% (S)

ref. 16 Schmeits PC et al. Investigating unexpected INRs: in search of the culprit -- adherence, interactions, genetics, and superwarfarin. Neth J Med 2009;67:76-8.	2 GA: D	A 68-year-old man was hospitalised in the ICU with recurrent pulmonary embolism. He had been treated with phenprocoumon for some years, but it had not been possible to identify the appropriate dose despite various dose adjustments. His genotype was found to be GA. He did not have any CYP-2C9 polymorphisms. NOTE: Genotyping was for the polymorphism 1173C>T.	

ref. 1**7**
Schalekamp et al. *VKORC1* and *CYP-2C9* genotypes and phenprocoumon anticoagulation status: interaction between both genotypes affects dose requirement. Clin Pharmacol Ther 2007;81:185-93.
	4
	
	GA: A
	AA: D
		281 patients; VKORC1 polymorphisms: 106x GG, 121x GA, 54x AA; phenprocoumon for 3-6 months; low target INR; no co-medication with impact on CYP2C9; correction for NSAID and antibiotic usage.
		
		- Risk of INR > 6 versus GG:
		  - GA: HR = 1.69 (NS)
		  - AA: HR = 2.28 (S)
		- Maintenance dose (mg/week) (mean all CYP2C9s):
		  - GG: 19.96
		  - GA: 16.11 (S by 19%)
		  - AA: 9.74 (S by 51%)
		- Time to stability (days) (mean of all CYP2C9s):
		  - GG: 71 (n=85)
		  - GA: 62 (n=100)
		  - AA: 71 (n=49)
		
		NOTE: Genotyping was for the polymorphism 1173C>T.
			Authors' conclusion:
			"The VKORC1 genotype modifies the effect of the CYP2C9 genotype on phenprocoumon dose requirements. A combination of polymorphisms of both genotypes is associated with a strongly increased risk of overanticoagulation."
			
			Maintenance dose versus GG:
			GA: 81% (S)
			AA: 49% (S)

ref. 18
Reitsma PH et al. A C1173T dimorphism in the VKORC1 gene determines coumarin sensitivity and bleeding risk. PLoS Med 2005;2:e312.
	3
	
	GA: D
	AA: A
		Case-control study including 110 patients with a history of bleeding on coumarin therapy and 220 patients with no history of bleeding. 48 cases (13 GG, 25 GA, 10 AA) and 81 controls (40 GG, 29 GA, 12 AA) used phenprocoumon. Co-medication was not known.
		
		- Risk of bleeding (major bleeding) versus GG:
		  - GA: OR = 2.7 (S)
		  - AA: OR = 2.6 (NS)
		  - GA+AA: OR = 2.6 (S)
		  - GA+AA (calculation including all 121 GA+AA controls): OR = 2.1 (S)
		- Mean dose required to achieve a certain INR:
		  - GG: 2.9 mg/day
		  - GA: 2.6 mg/day (NS by 10%)
		  - AA: 1.4 mg/day (S by 52%)
		
		Phenprocoumon had a greater effect on the risk of bleeding in carriers of an A-allele than acenocoumarol.
		
		NOTE: Genotyping was for the polymorphism 1173C>T.
			Authors' conclusion:
			"The results, although based on a small sample size of individuals with bleeding, support the suggestion that the bleeding risk for T-carriers is higher in phenprocoumon than in acenocoumarol users. If this finding is confirmed in additional studies and extended to more frequently occurring and clinically relevant cases of non-major bleeding, it may imply that CT and TT carriers should be preferentially treated with acenocoumarol."
			
			Maintenance

ref. 18, continuation			**dose versus GG:** GA: 90% AA: 48% (S)

[#] In these cases, there was a significant difference between GG and GA or AA, but the clinical effect was more favourable for GA or AA than for GG. As the purpose of classification of the severity of the effect is to classify negative effects, code AA is used for a positive effect.

Risk group	Use of CYP2C9 inhibitors, CYP2C9 polymorphisms

Comments:

- Articles relating to VKORC1 gene variations that led to acenocoumarol resistance were not included, because the prevalence of these VKORC1 gene variations is very low.
  The only articles included from 2007 were those that either showed a clinical effect or an effect size of separate VKORC1 phenotypes on dose or kinetics, because articles that only showed that VKORC1 has an effect on kinetics or dose did not supply new information.
  From 2011, articles investigating the effect on dose or kinetics were only included if the patient number was 100 or more and if data were available per genotype. Other articles on dose or kinetics supplied insufficient new information. All articles with data on bleeding and/or INR > 6 were included, as were articles comparing genotype-guided treatment to non-genotype-guided treatment and articles providing new information on the studies in such articles.
- **Dosing algorithms:**
  - van Schie RM et al. Loading and maintenance dose algorithms for phenprocoumon and acenocoumarol using patient characteristics and pharmacogenetic data. Eur Heart J 2011;32:1909-17.
    An algorithm for the phenprocoumon maintenance dose was developed on the basis of data from 559 phenprocoumon users with target INRs of 2.0-3.5. The algorithm was validated in an independent dataset including 229 phenprocoumon users, whose height and body weight parameters were not known. As phenprocoumon has a long half-life (160 hours), a separate loading dose is required. The loading dose is divided over the first 3 days and is calculated from the calculated maintenance dose using the formula mentioned below. The algorithm explained 55.9% of the variation in dose requirement, where the VKORC1 polymorphism explained 34.1% of the variation. The mean absolute error in the calculated maintenance dose was 0.45 mg/day. These numbers were 59.4% and 0.46 mg/day respectively for the validation set. A randomised controlled trial is required to test whether the use of this algorithm leads to improvement of control and safety of phenprocoumon therapy.
    The algorithm found was:
    $\sqrt{}$ (mean maintenance dose (mg/week)) = 2.874 – 0 (if CYP2C9*1/*1) – 0.259 (if CYP2C9*1/*2) – 0.342 (if CYP2C9*1/*3) – 0.447 (if CYP2C9*2/*2) – 0.684 (if CYP2C9*2/*3) – 0.681 (if CYP2C9*3/*3) – 0 (if VKORC1 GG) – 0.601 (if VKORC1 GA) – 1.394 (if VKORC1 AA) – 0.015 * age (years) + 0.026 (if female) + 0.011 * height (cm) + 0.008 * body weight (kg) – 0.345 (if amiodarone user)
    Formula to calculate the loading dose based on the calculated maintenance dose:
    maintenance dose (mg/day) = $(D_1*e^{-2k} + D_2*e^{-k} + D_3)/(1-e^{-k})$
    where D_1, D_2 and D_3 represent the dose on day 1, 2 and 3 respectively and where the elimination rate constant k is equal to $\ln(2)/t_{1/2}$.
    Loading doses used:

Loading dose (in mg)	Calculated maintenance dose (mg/day)
3-3-3	< 1.04
6-3-3	1.04-1.31
6-6-3	1.31-1.61
6-6-6	1.61-1.85
9-6-6	1.85-2.92
9-9-6	> 2.92

    The loading dose was always selected to lead to the lower limit (LLN) of the maintenance dose range specified.
    NOTE: The polymorphism 1173C>T was determined in this study.
  - Geisen C et al. Prediction of phenprocoumon maintenance dose and phenprocoumon plasma concentration by genetic and non-genetic parameters. Eur J Clin Pharmacol 2011;67:371-81.
    An algorithm for the phenprocoumon maintenance dose was developed based on data from 75 phenprocoumon users with target INR of 2.0-3.0. The algorithm was not validated in an independent

dataset. The algorithm explained 48.6% of the variation in dose requirement, where the VKORC1 polymorphism explained 37.6% of the variation. The mean absolute error in the calculated maintenance dose was 0.52 mg/day. Passing-Bablok regression analysis showed a good correlation between the actual and calculated phenprocoumon dose (r=0.701).
The algorithm found in the study was:
√ (maintenance dose (mg/day)) = 0.460 + 0.238 (if VKORC1 GG) – 0.271 (if VKORC1 AA) + 0.007 * height (cm) – 0.004*age (in years)

- Puehringer H et al. VKORC1 -1639G>A and CYP2C9*3 are the major genetic predictors of phenprocoumon dose requirement. Eur J Clin Pharmacol 2010;66:591-8.
An algorithm for the phenprocoumon maintenance dose was developed based on the data from 185 phenprocoumon users with target INR of 2.0-3.0. The algorithm was not validated in an independent dataset. The algorithm explained 31% of the variation in dose requirement, where the VKORC1 polymorphism explained 14.2% of the variation.
√ (maintenance dose (mg/week)) = 4.823 – 0.4148 * the number of VKORC1 A alleles – 0.0187 * age (in years) – 0.5535 * the number of CYP2C9 *3 alleles – 0.2503 * the number of CYP2C9 *2 alleles + 0.057 * body weight (kg)

Date of literature search: 18 July 2018.

	Genotype	Code	Gene-drug interaction	Action	Date
Dutch Pharmacogenetic Working Group decision	GA	4D	Yes	No	10 September 2018
	AA	4D	Yes	Yes	

Mechanism:
Coumarins exert their effect by inhibition of enzyme activity of the vitamin K 2,3-epoxide reductase complex subunit 1 (VKORC1). Mutations in the VKORC1 gene may lead to reduced production of the VKORC1 protein. This requires a lower coumarin dose for inhibition of this protein.
VKORC1 regenerates reduced vitamin K (vitamin K 2,3-epoxide) to the active oxidised form (vitamin K hydroquinone). Vitamin K is an essential cofactor for carboxylation of glutamic acid residues on coagulation factors II, VII, IX and X and the anticoagulation proteins C, S and Z. Inhibition of VKORC1 therefore results in reduced coagulation.

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 to genotype 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 < NNG ≤ 1000	+	
• 10 < NNG ≤ 100	++	
• NNG ≤ 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+	3+
Corresponding Clinical Implication Score:		Beneficial