



## CYP2C9: phenprocoumon#

2523 to 2529‡

\*1 = no CYP2C9 gene variant, normal activity, \*2 = CYP2C9 gene variant with decreased activity, \*3 = CYP2C9 gene variant with strongly decreased activity,  $Cl_{or}$  = oral clearance, 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 = non-significant, NSAID = non-steroid anti-inflammatory drug, 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 = relative risk, S = significant, VKA = vitamin K antagonist, VKORC1 = vitamin K epoxide reductase complex 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.

### Brief summary and justification of choices:

Phenprocoumon consists of a racemic mixture. The S-enantiomer is 2-5x more potent than the R-enantiomer for the effect on coagulation. The S-enantiomer is almost completely metabolised by CYP2C9. The R-enantiomer is mainly metabolised by CYP2C9 and CYP3A4. A proportion of phenprocoumon is excreted in unchanged form. CYP2C9 gene variants leading to decreased metabolic capacity of the enzyme, cause increased S-phenprocoumon plasma concentrations and to a lesser extent increased R-phenprocoumon plasma concentrations. As confirmed in literature, these gene variants reduce the required phenprocoumon dose (Camilleri 2024, Schneider 2020, Abduljalil 2013 (\*1/\*3), Cadamuro 2010, Schalekamp 2007, and Schalekamp 2004). However, the influence of CYP2C9 variants on phenprocoumon plasma concentrations and hence required phenprocoumon dose is relatively small and does not reach significance in many of the published studies (Brehm 2016, Abduljalil 2013 (\*1/\*2, \*2/\*2, \*2/\*3), Brehm 2013, Geisen 2011, Qazim 2009, zu Schwabedissen 2006, Visser 2005, Visser 2004, and Hummers-Pradier 2003). Despite this relative small influence on the phenprocoumon dose, 4 studies report clinical consequences of the presence of a CYP2C9 gene variant. Hummers-Pradier 2003 showed an increased bleeding risk for \*1/\*3+\*2/\*3 in patients treated for a mean of 5 years. Three Dutch studies reported an increased risk of severe overanticoagulation (INR > 6), two in the first 6 treatment months (Schalekamp 2007 and Schalekamp 2004) and one only in patients using NSAIDs (Visser 2005). A study showed no significant difference in clinical effect for all genotypes combined when using a pharmacogenetic dosing algorithm for the first 5-7 days (Verhoef 2013). 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 (Zhang 2017). 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, the KNMP Pharmacogenetics Working Group decided to recommend a dose reduction for genotypes with a substantial influence on the required phenprocoumon dose (i.e. a required dose reduction of at least 25% of the normal dose).

Calculated decreases in maintenance dose and final recommendations

- |       |  |
|-------|--|
| *1/*2 | The weighted mean of the calculated required decrease in maintenance dose for *1/*2 is a decrease to 87% of the normal maintenance dose (range 76-105%, median 82%) (based on a total of 213 *1/*2 from 7 studies) (Schneider 2020, Abduljalil 2013, Brehm 2013, Cadamuro 2010, Qazim 2009, Schalekamp 2004, and Hummers-Pradier 2003). Since the required decrease is small, the KNMP Pharmacogenetics Working Group decided not to recommend adjustment of therapy for *1/*2 (yes/no-interaction). |
| *1/*3 | The weighted mean of the calculated required decrease in maintenance dose for *1/*3 is a decrease to 80% of the normal maintenance dose (range 54-90%, median 79%) (based on a total of 141 *1/*3 from 7 studies) (Schneider 2020, Abduljalil 2013, Brehm 2013, Cadamuro 2010, Qazim 2009, Schale-   |

kamp 2004, and Hummers-Pradier 2003). Since the required decrease is small, the KNMP Pharmacogenetics Working Group decided not to recommend adjustment of therapy for \*1/\*3 (yes/no-interaction).

IM OTHER	There are no data on the required dose reduction for IM OTHER. Because the required dose decrease was small for both *1/*2 and *1/*3, the KNMP Pharmacogenetics Working Group decided not to recommend adjustment of therapy for IM OTHER (yes/no-interaction).
*2/*2	The weighted mean of the calculated required decrease in maintenance dose for *2/*2 is a decrease to 67% of the normal maintenance dose (range 39-108%, median 71%) (based on a total of 17 *2/*2 from 6 studies) (Schneider 2020, Abduljalil 2013, Brehm 2013, Cadamuro 2010, Qazim 2009, and Schalekamp 2004). Because phenprocoumon is dosed in multiples of 3 mg (or 1.5 mg) and doses tend to be around 15 mg per week, this was translated to a decrease to 2/3 <sup>rd</sup> of the normal dose, to be more achievable in clinical practice. Because of this, the KNMP Pharmacogenetics Working Group decided to recommend adjustment of the therapy for *2/*2 by starting with 2/3 <sup>rd</sup> of the normal dose (yes/yes-interaction). The KNMP Pharmacogenetics Working Group also decided to recommend additional monitoring in hospitals, where patients are initiated on anticoagulant therapy by residents or internists.
*2/*3	The weighted mean of the calculated required decrease in maintenance dose for *2/*3 is a decrease to 68% of the normal maintenance dose (range 55-80%, median 68%) (based on a total of 16 *2/*3 from 5 studies) (Schneider 2020, Abduljalil 2013, Brehm 2013, Cadamuro 2010, and Schalekamp 2004). Because phenprocoumon is dosed in multiples of 3 mg (or 1.5 mg) and doses tend to be around 15 mg per week, this was translated to a decrease to 2/3 <sup>rd</sup> of the normal dose, to be more achievable in clinical practice. Because of this, the KNMP Pharmacogenetics Working Group decided to recommend adjustment of the therapy for *2/*3 by starting with 2/3 <sup>rd</sup> of the normal dose (yes/yes-interaction). The KNMP Pharmacogenetics Working Group also decided to recommend additional monitoring in hospitals, where patients are initiated on anticoagulant therapy by residents or internists.
*3/*3	The calculated required decrease in maintenance dose for *3/*3 is a decrease to 65% of the normal maintenance dose (based on 2 *3/*3 from 1 study) (Schalekamp 2004). Because phenprocoumon is dosed in multiples of 3 mg (or 1.5 mg) and doses tend to be around 15 mg per week, this was translated to a decrease to 2/3 <sup>rd</sup> of the normal dose, to be more achievable in clinical practice. Because of this, the KNMP Pharmacogenetics Working Group decided to recommend adjustment of the therapy for *3/*3 by starting with 2/3 <sup>rd</sup> of the normal dose (yes/yes-interaction). The KNMP Pharmacogenetics Working Group also decided to recommend additional monitoring in hospitals, where patients are initiated on anticoagulant therapy by residents or internists.
PM OTHER	There are no data on the required dose reduction for PM OTHER. For PM OTHER, the KNMP Pharmacogenetics Working Group decided to recommend the same dose reduction as for *2/*2, *2/*3 and *3/*3, i.e. to start with 2/3 <sup>rd</sup> of the normal dose (yes/yes-interaction).

You can find a detailed overview of the effects per genotype or genotype group in the background information text of the corresponding gene-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.

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

The KNMP Pharmacogenetics Working Group considers genotyping before starting phenprocoumon to be potentially beneficial for drug safety. Genotyping can be considered on an individual patient basis. If, however, the genotype is available, the DPWG recommends adhering to the gene-drug guideline.

The clinical implication of the gene-drug interaction scores 1 out of the maximum of 10 points (with pre-emptive genotyping considered to be potentially beneficial for scores ranging from 0 to 2 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 with CYP2C9 variants (Schalekamp 2007, Visser 2005, and Schalekamp 2004). In addition, INR > 8 was observed in a case report (also severity code D corresponding to CTCAE grade 3) (Bohrer 2006). 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).

Three studies confirmed CYP2C9 variants to result in a severe clinical effect (score of D corresponding to CTCAE grade 3) (Schalekamp 2007, Visser 2005, and Schalekamp 2004). However, in all of these studies, the code referred to INR ≥ 6. 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, these 3 studies were not counted as contributing to the level of evidence supporting an associated clinical effect grade ≥ 3, leaving 0 studies to contribute to this level of evidence. This results in 0 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 (only points for at least one publication with level of evidence score ≥ 3).

Because there are no studies showing an increased risk of major bleeding, the number needed to genotype could not be determined and is likely to be over 1000. This results in 0 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  $\geq 3$  (only points for  $NNG \leq 1000$ ).

The Summary of Product Characteristics (SmPC) of phenprocoumon does not mention any CYP2C9 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 (only points for at least one genotype/phenotype mentioned in the SmPC).

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																																												
<p><b>ref. 1</b> Camilleri E et al. Genetic polymorphisms and major bleeding risk during vitamin K antagonists treatment: The BLEEDS case-cohort. Pharmacotherapy 2024;44:416-24. PMID: 38686648.</p>	3	<p>Of 16,570 patients treated with VKAs, 326 developed major bleeding. A case-cohort study was assembled with all genotyped cases (n = 239) and 783 patients from a random subcohort. Most patients used phenprocoumon (73% in the full cohort, 78% in the cases, and 75% in the subcohort). Bleeding was defined as major if it was fatal, intracranial, an objectively diagnosed joint bleed, a bleeding event in a critical organ, or if it led to a blood transfusion or to a hospital admission. Comedication affecting phenprocoumon was not excluded.</p> <p>Genotyping of the cases (complete follow-up):  <table border="0"> <tr> <td>whole group (phenprocoumon and acenocoumarol users)</td> <td>phenprocoumon users only</td> </tr> <tr> <td>- 169x *1/*1</td> <td>- 132x *1/*1</td> </tr> <tr> <td>- 62x (*1/*2 or *1/*3)</td> <td>- 46x (*1/*2 or *1/*3)</td> </tr> <tr> <td>- 8x (*2/*2 or *2/*3 or *3/*3)</td> <td>- 8x (*2/*2 or *2/*3 or *3/*3)</td> </tr> </table> </p> <p>Results for the whole group (mainly phenprocoumon users, but also acenocoumarol and to a lesser extent warfarin users):</p> <table border="1"> <thead> <tr> <th colspan="4">Incidence rate of major bleeding per 100 patient years compared to *1/*1:</th> </tr> <tr> <th>follow-up</th> <th>*2/*2+ *2/*3+*3/*3</th> <th>*1/*2+*1/*3</th> <th>value for *1/*1</th> </tr> </thead> <tbody> <tr> <td>complete</td> <td>NS</td> <td>NS</td> <td>1.6</td> </tr> <tr> <td></td> <td colspan="2">Note: Results were also NS for the subgroup of phenprocoumon users.</td> <td></td> </tr> <tr> <td>first 6 months</td> <td>NS</td> <td>NS</td> <td>2.0</td> </tr> <tr> <td>first 3 months</td> <td>NS</td> <td>NS</td> <td>2.7</td> </tr> <tr> <td>first 2 months</td> <td>NS</td> <td>NS</td> <td>2.9</td> </tr> <tr> <td>first month</td> <td>NS</td> <td>NS</td> <td>3.6</td> </tr> <tr> <td colspan="4">Note: *2/*2+ *2/*3+*3/*3 had a lower dose requirement than *1/*1 (S).</td> </tr> </tbody> </table> <p>Note: Genotyping was for *2 and *3. These are the most important gene variants in this Dutch population.</p>	whole group (phenprocoumon and acenocoumarol users)	phenprocoumon users only	- 169x *1/*1	- 132x *1/*1	- 62x (*1/*2 or *1/*3)	- 46x (*1/*2 or *1/*3)	- 8x (*2/*2 or *2/*3 or *3/*3)	- 8x (*2/*2 or *2/*3 or *3/*3)	Incidence rate of major bleeding per 100 patient years compared to *1/*1:				follow-up	*2/*2+ *2/*3+*3/*3	*1/*2+*1/*3	value for *1/*1	complete	NS	NS	1.6		Note: Results were also NS for the subgroup of phenprocoumon users.			first 6 months	NS	NS	2.0	first 3 months	NS	NS	2.7	first 2 months	NS	NS	2.9	first month	NS	NS	3.6	Note: *2/*2+ *2/*3+*3/*3 had a lower dose requirement than *1/*1 (S).				<p>Author's conclusion: "For the CYP2C9 and GGCX variants instead, the major bleeding risk was around unity."</p>
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<p><b>ref. 2</b> Just KS et al. Adverse drug reactions in the emergency department: is there a role for pharmacogenomic profiles at risk?- Results from the</p>	3	<p>60 patients admitted to the emergency department with adverse drug reactions suspected to be caused by phenprocoumon were compared to 716 patients admitted to the emergency department with adverse drug reactions suspected to be caused by other drugs.</p> <p>All patients had symptoms, that were seen in a possible, probable, or certain relation to a drug (definition of an adverse drug reaction) according to the WHO-Uppsala Monitoring Centre (UMC) system for causality assessment.</p>	<p>Author's conclusion: "The frequency distribution of the CYP2C9 phenotype did not differ significantly in the subgroup of the phenprocoumon-</p>																																												

<p>ADRED study. J Clin Med 2020;9:1801. PMID: 32527038.</p> <p><b>ref. 2, continuation</b></p>	<p>*1/*2+ *1/*3+ IM OTHER : AA *2/*2+ *2/*3+ *3/*3+ PM OTHER : AA</p>	<p>Comedication affecting phenprocoumon was not excluded.</p> <p>Results:</p> <table border="1" data-bbox="496 219 1225 497"> <tr> <td colspan="2">Results for emergency department admitted patients with phenprocoumon-induced adverse drug reactions compared to emergency department admitted patients with adverse drug reactions induced by other drugs:</td> </tr> <tr> <td>distribution of the *1/*1, *1/*2+*1/*3+IM OTHER, and *2/*2+*2/*3+*3/*3+PM OTHER genotype groups over the patients</td> <td>NS</td> </tr> </table> <p>Note: Genotyping was for 10 CYP2C9 variants. Gene variants *2, *3, *11, and *12 were found. So, genotyping included the most important gene variants in this German population (*2 and *3).</p>	Results for emergency department admitted patients with phenprocoumon-induced adverse drug reactions compared to emergency department admitted patients with adverse drug reactions induced by other drugs:		distribution of the *1/*1, *1/*2+*1/*3+IM OTHER, and *2/*2+*2/*3+*3/*3+PM OTHER genotype groups over the patients	NS	<p>suspecting adverse drug reactions, compared to the rest.”</p>																																																														
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<p><b>ref. 3</b> Schneider KL et al. Phenprocoumon dose requirements, dose stability and time in therapeutic range in elderly patients with CYP2C9 and VKORC1 polymorphisms. Front Pharmacol 2020;10:1620. PMID: 32047440.</p>	<p>3</p> <p>*1/*3+ *2/*3: A *1/*2+ *2/*2: A</p>	<p>Data of 209 phenprocoumon treated patients, aged ≥ 60 years and with at least two INR values within the previous three months (the study period), were retrospectively analysed. The vast majority of the patients could be attributed to the maintenance phase as they provided more retrospective data than the required three months. Information on the phenprocoumon dose was lacking for 3 *1/*1 patients and 1 *1/*2 patient. In addition, for 2 patients only one weekly phenprocoumon dose was known.</p> <p>Comedication affecting phenprocoumon was not excluded.</p> <p>Genotyping: - 145x *1/*1 (of whom 142 with a known dose) - 36x *1/*2 (of whom 35 with a known dose) - 1x *2/*2 - 23x *1/*3 - 4x *2/*3</p> <p>Results:</p> <table border="1" data-bbox="496 1234 1225 2065"> <thead> <tr> <th colspan="6">Results compared to *1/*1:</th> </tr> <tr> <th></th> <th>*2/*3</th> <th>*1/*3</th> <th>*2/*2</th> <th>*1/*2</th> <th>value for *1/*1</th> </tr> </thead> <tbody> <tr> <td>mean phenprocoumon dose (in mg /week)</td> <td>x 0.68</td> <td>x 0.79</td> <td>x 1.08</td> <td>x 0.82</td> <td>14.4</td> </tr> <tr> <td></td> <td colspan="4">S for *1/*3+*2/*3 versus *1/*2+*2/*2 versus *1/*1</td> <td></td> </tr> <tr> <td>mean INR</td> <td colspan="4">NS for *1/*3+*2/*3 versus *1/*2+*2/*2 versus *1/*1</td> <td>2.3</td> </tr> <tr> <td>standard deviation of weekly dose per patient (intra-individual variability)</td> <td colspan="2">x 1.02</td> <td colspan="2">x 0.41</td> <td>1.27</td> </tr> <tr> <td></td> <td colspan="4">S for *1/*3+*2/*3 versus *1/*2+*2/*2 versus *1/*1</td> <td></td> </tr> <tr> <td>% of patients with a constant dose</td> <td colspan="4">trend for *1/*3+*2/*3 versus *1/*2+*2/*2 versus *1/*1 (trend for a higher percentage in *1/*3+*2/*3) (p = 0.074) (NS)</td> <td>20.7</td> </tr> <tr> <td>median % of time in therapeutic range</td> <td colspan="2">x 1.33</td> <td colspan="2">x 1.05</td> <td>75.4</td> </tr> <tr> <td></td> <td colspan="4">S for *1/*3+*2/*3 versus *1/*2+*2/*2 versus *1/*1</td> <td></td> </tr> <tr> <td>% of patients with 100% of time in therapeutic range</td> <td colspan="4">trend for *1/*3+*2/*3 versus *1/*2+*2/*2 versus *1/*1 (lowest percentage for *1/*1) (p = 0.071) (NS)</td> <td>22.8</td> </tr> </tbody> </table>	Results compared to *1/*1:							*2/*3	*1/*3	*2/*2	*1/*2	value for *1/*1	mean phenprocoumon dose (in mg /week)	x 0.68	x 0.79	x 1.08	x 0.82	14.4		S for *1/*3+*2/*3 versus *1/*2+*2/*2 versus *1/*1					mean INR	NS for *1/*3+*2/*3 versus *1/*2+*2/*2 versus *1/*1				2.3	standard deviation of weekly dose per patient (intra-individual variability)	x 1.02		x 0.41		1.27		S for *1/*3+*2/*3 versus *1/*2+*2/*2 versus *1/*1					% of patients with a constant dose	trend for *1/*3+*2/*3 versus *1/*2+*2/*2 versus *1/*1 (trend for a higher percentage in *1/*3+*2/*3) (p = 0.074) (NS)				20.7	median % of time in therapeutic range	x 1.33		x 1.05		75.4		S for *1/*3+*2/*3 versus *1/*2+*2/*2 versus *1/*1					% of patients with 100% of time in therapeutic range	trend for *1/*3+*2/*3 versus *1/*2+*2/*2 versus *1/*1 (lowest percentage for *1/*1) (p = 0.071) (NS)				22.8	<p>Author's conclusion: "Our analyses support the results of previous investigations regarding genotype-associated dose requirements and raise the hypothesis that dose stability and anticoagulation quality may be increased in CYP-2C9*3 carriers."</p> <p>(Maintenance) dose versus *1/*1: *1/*2: 82% *1/*3: 79% *2/*2: 108% *2/*3: 68%</p>
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ref. 3, continuation		<p>Results were comparable if only data from patients with complete dose information were used.</p> <p>Note: Genotyping was for *2 and *3. These are the most important gene variants in this German population.</p>																												
<p><b>ref. 4</b> Zhang Y et al. Age-stratified outcome of a genotype-guided dosing algorithm for acenocoumarol and phenprocoumon. J Thromb Haemost 2017;15:454-464. PubMed PMID: 27992949.</p>	<p>3</p> <p>genotype-guided versus not genotype-guided therapy patients</p>	<p>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 &lt; 75 years of age and 24 patients ≥ 75 years of age) and 80 received control treatment (63 patients &lt; 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 &lt; 75 years of age and 16 patients ≥ 75 years of age) and 58 in the control group (47 patients &lt; 75 years of age and 11 patients ≥ 75 years of age). All INRs were measured during the first 12 weeks of treatment.</p> <p>Patient characteristics in the different groups were similar, except for patients &lt; 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.</p> <p>Genotyping: - 107x *1/*1 - 27x *1/*2 - 18x *1/*3 - 4x *2/*2 - 2x *2/*3 - 1x genotype unknown (clinical algorithm, &lt; 75 years)</p> <p>Results:</p> <table border="1" data-bbox="497 1263 1225 2072"> <thead> <tr> <th colspan="4">Genotype-based algorithm versus clinical algorithm:</th> </tr> <tr> <th></th> <th></th> <th></th> <th>value for the clinical algorithm</th> </tr> </thead> <tbody> <tr> <td rowspan="6">% of time in the therapeutic range</td> <td>&lt; 75 years, no CYP2C9 and VKORC1 variants</td> <td>NS</td> <td>53.9%</td> </tr> <tr> <td>&lt; 75 years, one CYP2C9 or VKORC1 variant</td> <td>NS</td> <td>63.0%</td> </tr> <tr> <td>&lt; 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)</td> <td>55.6%</td> </tr> </tbody> </table>	Genotype-based algorithm versus clinical algorithm:							value for the clinical algorithm	% of time in the therapeutic range	< 75 years, no CYP2C9 and VKORC1 variants	NS	53.9%	< 75 years, one CYP2C9 or VKORC1 variant	NS	63.0%	< 75 years, two or more CYP2C9 and/or VKORC1 variants	+ 14.0% (S)	52.1%	≥ 75 years, no CYP2C9 and VKORC1 variants	NS	56.0%	≥ 75 years, one CYP2C9 or VKORC1 variant	NS	67.2%	≥ 75 years, two or more CYP2C9 and/or VKORC1 variants	significance could not be determined (n = 1 in the control)	55.6%	<p>Author's conclusion: "The results support the use of genotype-guided dosing for phenprocoumon in patients &lt; 75 years. For patients ≥ 75 years the phenprocoumon algorithm should be revised and further tested."</p>
Genotype-based algorithm versus clinical algorithm:																														
			value for the clinical algorithm																											
% of time in the therapeutic range	< 75 years, no CYP2C9 and VKORC1 variants	NS	53.9%																											
	< 75 years, one CYP2C9 or VKORC1 variant	NS	63.0%																											
	< 75 years, two or more CYP2C9 and/or VKORC1 variants	+ 14.0% (S)	52.1%																											
	≥ 75 years, no CYP2C9 and VKORC1 variants	NS	56.0%																											
	≥ 75 years, one CYP2C9 or VKORC1 variant	NS	67.2%																											
	≥ 75 years, two or more CYP2C9 and/or VKORC1 variants	significance could not be determined (n = 1 in the control)	55.6%																											

ref. 4, continuation	< 75 years: AA#	group)		
		< 75 years	+ 9.5% (S)	55.7%
		≥ 75 years	- 17.9% (S)	63.3%
		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).		
genotype-guided versus not genotype-guided therapy , patients ≥ 75 years: A	% of time with a supratherapeutic INR (> 3.0)	< 75 years, no CYP2C9 and VKORC1 variants	NS	16.1%
		< 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 subtherapeutic 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.				

ref. 4, continuation		calculated dose for the patients in the genotype-guided 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 CYP2C9 and VKORC1 variants	+ 0.60 (S)	1.8			
	≥ 75 years, one CYP2C9 or VKORC1 variant	NS	1.9			
	≥ 75 years, two or more CYP2C9 and/or VKORC1 variants	- 0.40 (S)	1.7			
	< 75 years	- 0.20 (S)	2.3			
	≥ 75 years	NS	1.8			
	calculated dose for the patients in the control group (in mg/day)	< 75 years, no CYP2C9 and VKORC1 variants	+ 0.7 (S)	2.9		
		< 75 years, one CYP2C9 or VKORC1 variant	NS	2.3		
		< 75 years, two or more CYP2C9 and/or VKORC1 variants	+ 0.6 (S)	1.6		
		≥ 75 years, no CYP2C9 and VKORC1 variants	- 0.6 (S)	2.2		
		≥ 75 years, one CYP2C9 or VKORC1 variant	NS	1.8		
		≥ 75 years, two or more CYP2C9 and/or VKORC1 variants	not determined			
		< 75 years	NS	2.2		
		≥ 75 years	trend for a decrease (p = 0.10) (NS)	1.9		
		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.				
ref. 5 Brehm K et al. Genetic variations of phenprocoumon metabolism in patients with ventricular assist devices. Eur J Cardiothorac Surg 2016;50:275-80.	3	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			Author's conclusion: "CYP2C9 polymorphisms showed no effect on phenprocoumon doses."	

<p>PubMed PMID: 26984978.</p> <p><b>ref. 5, continuation</b></p>	<p>(*1/*3+ *2/*3+ *3/*3): AA</p> <p>(*1/*2+ *2/*2+ *2/*3): AA</p>	<p>the patients receiving a ventricular assist device in the same period were deceased and not included.</p> <p>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.</p> <p>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 infarction, 1 central retinal artery occlusion and 1 pulmonary embolism.</p> <p>High complication (major bleeding or thromboembolism) rates were observed particularly in the early post-operative period. Relevant co-medication was not excluded.</p> <p>The influence of genotypes on the occurrence of adverse events was evaluated by univariate logistic regression analysis.</p> <p>Genotyping: - 39x *1/*1 - 13x *1/*2 - 8x *1/*3 - 1x *2/*2 - 1x *2/*3 - 1x *3/*3</p> <p>Results:</p> <table border="1" data-bbox="496 1014 1225 1267"> <thead> <tr> <th colspan="3">Results compared to *1/*1:</th> </tr> <tr> <th></th> <th>*2-allele</th> <th>*3-allele</th> </tr> </thead> <tbody> <tr> <td>bleeding events</td> <td>NS</td> <td>NS</td> </tr> <tr> <td>thromboembolic events</td> <td>NS</td> <td>NS</td> </tr> <tr> <td>dose corrected INR increase during the loading phase</td> <td>NS</td> <td>NS</td> </tr> <tr> <td>phenprocoumon maintenance dose</td> <td>NS</td> <td>NS</td> </tr> </tbody> </table> <p>Note: Genotyping was for *2 and *3. These are the most important gene variants in this German population.</p>	Results compared to *1/*1:				*2-allele	*3-allele	bleeding events	NS	NS	thromboembolic events	NS	NS	dose corrected INR increase during the loading phase	NS	NS	phenprocoumon maintenance dose	NS	NS	
Results compared to *1/*1:																					
	*2-allele	*3-allele																			
bleeding events	NS	NS																			
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dose corrected INR increase during the loading phase	NS	NS																			
phenprocoumon maintenance dose	NS	NS																			
<p><b>ref. 6</b> Verhoef TI et al. A randomized trial of genotype-guided dosing of acenocoumarol and phenprocoumon. N Engl J Med 2013;369:2304-12. PubMed PMID: 24251360.</p>	<p>3</p> <p>genotype-</p>	<p>Patients who had not previously received VKAs were treated with phenprocoumon for a period of 12 weeks. Treatment during the first 5-7 days was based on an algorithm in which CYP2C9 and VKORC1 genotypes were included (n = 83), or on an algorithm using only clinical information (n = 81). The INR target was 2.0-3.0. Relevant co-medication was not excluded. Amiodarone use was incorporated in the dose algorithm. Patients with venous thromboembolism (17%) were often given low molecular weight heparin until a therapeutic INR was achieved.</p> <p>Genotyping: - 112x *1/*1 - 28x *1/*2 - 18x *1/*3 - 4x *2/*2 - 2x *2/*3</p> <p>Genotype-based algorithm compared to clinical algorithm: - no increase in the time that the INR was in the therapeutic range during the entire treatment (NS) - no significant increase in the time that the INR was in the</p>	<p>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."</p>																		

**ref. 6, continuation**

guided versus not genotype-guided therapy : AA

therapeutic range in the first 4 weeks, but there was a trend for an elevation by 19% (from 41.2% to 49.0%; p = 0.05) (NS)

- no difference in the incidence of adverse events and thromboembolism (NS)
- no difference in the percentage of the patients with an INR ≥ 4, the percentage of the time with an INR ≥ 4 or < 2, the time required to achieve an INR in the therapeutic range and the time required to achieve a stable dose (NS)

If the data for acenocoumarol and phenprocoumon were combined, the percentage of time that the INR was in the therapeutic range during the first 4 weeks of the treatment was higher for the genotype-based algorithm than for the clinical algorithm (52.8% resp. 47.5% of the time) (S). There was no difference 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:

Genotype-based algorithm versus clinical algorithm:			
	genotype group	first 4 weeks	first 12 weeks
% of time in the therapeutic range	no CYP2C9 and VKORC1 variants	+ 14.68% (S, but only a trend after Bonferroni correction (significance for p < 0.001) (NS, p = 0.002))	trend for an increase, p = 0.087 (NS)
	one or more CYP2C9 variants and no VKORC1 variant	NS	NS
	no CYP2C9 variants and one VKORC1 variant	NS	NS
	one or more CYP2C9 variants and one VKORC1 variant	NS	NS
	no CYP2C9 variants and two VKORC1 variants	NS	NS
	one or more CYP2C9 variants and two VKORC1 variants	NS	NS
% of time with a supra-therapeutic INR (> 3.0)	no CYP2C9 and VKORC1 variants	NS	NS
	one or more CYP2C9 variants and no VKORC1 variant	NS	NS

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-CYP2C9 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

Baranova EV et al. Dosing algorithms for vitamin K antagonists across VKORC1 and CYP2C9 genotypes. J Thromb Haemost 2017;15:465-472. PubMed PMID: 28063245.

ref. 6, continuation			no CYP2C9 variants and one VKORC1 variant	NS	NS	of the genotype-guided algorithm 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 VKAs separately and in the per-protocol dataset.			
			ref. 7 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	<p>A total of 278 patients with different INR target values received a stable dose of phenprocoumon. Relevant co-medication was not excluded. A pharmacokinetic/pharmacodynamic model found a significant effect of CYP3A inhibitors/inducers, but no significant effect of CYP2C9 inhibitors/inducers on the clearance.</p> <p>Genotyping:  - 172x *1/*1  - 61x *1/*2  - 36x *1/*3  - 5x *2/*2  - 4x *2/*3</p>		<p>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, co-medication with CYP3A modifiers (i.e. inhibitors</p>

<p><b>ref. 7, continuation</b></p>	<p>*1/*2: AA  *1/*3: A *2/*2: AA *2/*3: AA</p>	<p>Maintenance dose versus *1/*1: - *1/*2: decrease by 17% (from 14.74 to 12.30 mg per week) (NS for the sub-group with VKORC1 CC) - *1/*3: decrease by 20% (from 14.74 mg to 11.74 mg per week) (S for the sub-group with VKORC1 CC) - *2/*2: decrease by 32% (from 14.74 mg to 9.95 mg per week) (NS, significance not determined) - *2/*3: decrease by 45% (from 14.74 mg to 8.06 mg per week) (NS, significance not determined)</p> <p>A pharmacokinetic/pharmacodynamic model found a significant effect of the CYP2C9 alleles on the clearance. The contribution of CYP2C9 was lower than that of VKORC1. The model also demonstrated a longer time to achieve a stable plasma concentration for *3/*3 than for *1/*1.</p>	<p>or inducers) and presence of atrial fibrillation.”</p> <p>Maintenance dose versus *1/*1: *1/*2: 83% *1/*3: 80% *2/*2: 68% *2/*3: 55%</p>
<p><b>ref. 8</b> 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.</p>	<p>3      *1/*2: AA *1/*3: AA *2/*2: AA *2/*3: AA</p>	<p>A total of 175 patients with a mechanical heart valve prosthesis received phenprocoumon for an average of 6.7 years. The INR target was 2.5-3.5. Relevant co-medication was not excluded.</p> <p>Genotyping: - 109x *1/*1 - 38x *1/*2 - 24x *1/*3 - 3x *2/*2 - 1x *2/*3</p> <p>(genotype with *3) versus (genotype with *2) versus *1/*1: - no difference in the risk of major and minor bleeding (NS) - no difference in the risk of venous thromboembolism (NS)</p> <p>*2/*3 versus *2/*2 versus *1/*3 versus *1/*2 versus *1/*1: - no significant decrease in the maintenance dose (10.5 versus 12.0 versus 14.2 versus 16.6 versus 15.8 mg/week) (66% versus 76% versus 90% versus 105% versus 100%) (NS)</p>	<p>Authors' conclusion: “No influence of CYP2C9 polymorphism on phenprocoumon dosage and anticoagulation-related complications was found.”</p> <p>Maintenance dose versus *1/*1: *1/*2: 105% *1/*3: 90% *2/*2: 76% *2/*3: 66%</p>
<p><b>ref. 9</b> 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. PMID: 21110013.</p>	<p>4      *1/*2: A *1/*3: A *2/*3: A</p>	<p>A total of 75 patients on maintenance therapy with phenprocoumon. The INR target was 2.0-3.0. Relevant co-medication was present in 59% of the patients, but co-medication had no significant effect on the maintenance dose.</p> <p>Genotyping: - 48x *1/*1 - 18x *1/*2 - 8x *1/*3 - 1x *2/*3</p> <p>*2/*3 versus *1/*3 versus *1/*2 versus *1/*1: - increase in the median plasma concentration of phenprocoumon (5.1 versus 2.00 versus 2.02 versus 1.84 mg/L) (S) - no difference in the median maintenance dose (2.14 versus 2.25 versus 1.71 versus 2.14 mg/day) (NS)</p> <p>CYP2C9 genotype is an independent variable for the maintenance dose (multivariable regression analysis), but has a limited influence. CYP2C9 was not included in the final dose algorithm.</p>	<p>Authors' conclusion: “We did not detect an effect of CYP2C9 on phenprocoumon maintenance doses.”</p>
<p><b>ref. 10</b> Luxembourg B et al. Impact of pharmacokinetic (CYP2C9) and pharmacodynamic (VKORC1, F7,</p>	<p>3</p>	<p>A total of 54 patients who started treatment and 91 patients on maintenance therapy with phenprocoumon. The INR target was 2.0-3.0. The median initial dose was 18 mg divided over 3 days. No dose algorithm was used. Relevant co-medication was not excluded. Median measurement values were given.</p>	<p>Authors' conclusion: “Although Schalekamp et al. observed an increased risk of overanticoa-</p>

<p>GGCX, CALU, EPHX1) gene variants on the initiation and maintenance phases of phenprocoumon therapy. Thromb Haemost 2011;105:169-80. PMID: 21057703.</p> <p><b>ref. 10, continuation</b></p>	<p>(*1/*2 + *1/*3 + *2/*3 + *3/*3): AA#</p>	<p>Genotyping: Initiation phase: - 28x *1/*1 - 17x *1/*2 - 7x *1/*3 - 1x *2/*3 - 1x *3/*3</p> <p>Maintenance therapy: - 56x *1/*1 - 20x *1/*2 - 11x *1/*3 - 3x *2/*3 - 1x *3/*3</p> <p><i>Initiation phase:</i> (*2 or *3) versus *1/*1: - no difference in dose during the initiation phase (NS) - no difference in the first measured INR (NS) - decrease in the time to achieve stable INR by 43% (from 30 to 17 days) (S). The HR for achieving a stable INR at an earlier stage was 1.83 (95% CI: 1.05-3.18). - a 38% decrease in the number of visits to the thrombosis physician required before achieving a stable INR (from 8 to 5) (S) - no difference in the time to the first INR &gt; 3.0 (NS) - no difference in the percentage of the time that INR is &gt; 3.0 (NS)</p> <p><i>Maintenance therapy:</i> - no difference in the time that INR is &lt; 2.0 or &gt; 3.0 between (*2 or *3) and *1/*1 (NS)</p>	<p>gulation in carriers of the CYP2C9*2 or *3 allele during the initial weeks of phenprocoumon treatment, CYP2C9 defect allele status was not associated with adverse outcome parameters in the initiation and maintenance phases of phenprocoumon therapy in our study. CYP2C9 defect carriers even reached stable INRs significantly faster with a lower number of visits compared to wildtype carriers. However, the number of patients with the CYP2C9 *3/*3 genotype was very limited in our study."</p>
<p><b>ref. 11</b> Cadamuro J et al. Genetic determinants of acenocoumarol and phenprocoumon maintenance dose requirements. Eur J Clin Pharmacol 2010;66:253-60.</p>	<p>4</p> <p>*1/*2: A *1/*3: A *2/*2: A *2/*3: A</p>	<p>126 patients, 86x *1/*1, 21x *1/*2, 14x *1/*3, 3x *2/*2, 2x *2/*3, phenprocoumon for various indications and INR targets, significance is retained after correction for relevant co-medication;</p> <p>Maintenance dose (corrected for age, gender and last INR) versus *1/*1: - *1/*2: decrease by 18% from 15.81 to 12.96 mg/week (S for the trend) - *1/*3: decrease by 21% from 15.81 to 12.45 mg/week (S for the trend) - *2/*2: decrease by 57% from 15.81 to 6.72 mg/week (S for the trend) - *2/*3: decrease by 20% from 15.81 to 12.63 mg/week (S for the trend)</p> <p>CYP2C9*2 is an independent variable for the maintenance dose (multivariable regression analysis). Age, gender, last INR and VKORC1 and CYP2C9 genotypes together determine 55% of the variability in the maintenance dose.</p>	<p>Authors' conclusion: "These results reveal that interindividual variability in weekly phenprocoumon maintenance dose requirement is mainly dependent on the VKORC1 1173 C&gt;T and the CYP2C9*3 alleles. VKORC1 and CYP2C9 genotyping might provide helpful information to prevent serious bleeding events in subjects receiving phenprocoumon."</p> <p>Maintenance dose versus *1/*1: *1/*2: 82% *1/*3: 79% *2/*2: 43% *2/*3: 80%</p>
<p><b>ref. 12</b> Werner D et al. Pharmacogenetic characteristics of patients with complicated</p>	<p>3</p>	<p>Case-control study involving 60 cases with complicated anticoagulation on phenprocoumon (maintenance dose ≤ 1.5 mg/day (n = 46), overanticoagulation for ≥ 1 week following standard loading dose (mean 18.2 mg divided over the first 3 days) (n = 7) or INR unchanged for ≥ 1 week after stopping phenprocoumon (n = 7)), co-medication with an effect on the</p>	<p>Authors' conclusion: "The data suggest a fundamental role of VKORC1 haplotypes and a minor</p>

<p>phenprocoumon dosing. Eur J Clin Pharmacol 2009;65:783-8.</p> <p><b>ref. 12, continuation</b></p>	<p>*2/*2 + *2/*3 + *3/*3: A</p> <p>*1/*2 + *1/*3: AA</p>	<p>INR was not excluded;</p> <p>Case group versus control group:</p> <ul style="list-style-type: none"> <li>- percentage of patients with a variant allele is elevated by a factor 1.75 (95% CI 1.17-2.60)</li> <li>- percentage of *2/*2 + *2/*3 + *3/*3 is elevated by a factor 4.0 (95% CI 1.25-12.7)</li> <li>- no significant difference in percentage of *1/*2 + *1/*3 (NS)</li> </ul>	<p>role of CYP2C9 variants in the anti-coagulation property of phenprocoumon."</p>
<p><b>ref. 13</b> Qazim B et al. Dependency of phenprocoumon dosage on polymorphisms in the VKORC1 and CYP2C9 genes. J Thromb Thrombolysis 2009;28:211-4.</p>	<p>3</p> <p>*1/*2: AA</p> <p>*1/*3: AA</p> <p>*2/*2: AA</p>	<p>Cross-sectional study, 53 patients, 34x *1/*1, 11x *1/*2, 7x *1/*3, 1x *2/*2, maintenance therapy with phenprocoumon for various indications, co-medication that potentiates (n = 45) or weakens (n = 12) the effect of phenprocoumon is present;</p> <ul style="list-style-type: none"> <li>- no difference in INR values between the various genotypes</li> <li>- maintenance dose versus *1/*1: <ul style="list-style-type: none"> <li>- *1/*2: decrease by 24% from 13.5 to 10.2 mg/week (NS)</li> <li>- *1/*3: decrease by 46% from 13.5 to 7.3 mg/week (NS)</li> <li>- *2/*2: decrease by 61% from 13.5 to 5.3 mg/week (NS)</li> </ul> </li> </ul>	<p>Authors' conclusion: "Though VKORC1 and CYP2C9 polymorphisms influence the phenprocoumon dosage necessary to achieve therapeutic anticoagulation, anticoagulation is therapeutic if carefully monitored."</p> <p>Maintenance dose versus *1/*1: *1/*2: 76% *1/*3: 54% *2/*2: 39%</p>
<p><b>ref. 14</b> Schalekamp T et al. VKORC1 and CYP2C9 genotypes and phenprocoumon anticoagulation status: interaction between both genotypes affects dose requirement. Clin Pharmacol Ther 2007;81:185-93.</p>	<p>4</p> <p>*1/*2 + *2/*2: D</p> <p>*1/*3 + *2/*3 +</p>	<p>281 patients, 183x *1/*1, 56x *1/*2, 29x *1/*3, 5x *2/*2, 6x *2/*3 and 2x *3/*3, follow-up ≤ 180 days, target INR 2.0-3.5, relevant co-medication (NSAIDs, antibiotics) present, but had no effect on the results for maintenance dose and the time required to achieve stability; Doses were corrected for heart failure, gender and age. The risk of INR &gt; 6 was also corrected for the VKORC1 genotype.</p> <ul style="list-style-type: none"> <li>- VKORC1 has a significant effect on the dose reduction by CYP2C9 polymorphisms. Maintenance dose versus *1/*1: <ul style="list-style-type: none"> <li>- VKORC1 CC: <ul style="list-style-type: none"> <li>*1/*2 + *2/*2: decrease by 28% from 22.4 to 16.2 mg/week (S)</li> <li>*1/*3 + *2/*3 + *3/*3: decrease by 28% from 22.4 to 16.1 mg/week (S)</li> </ul> </li> <li>- VKORC1 CT: <ul style="list-style-type: none"> <li>*1/*2 + *2/*2: decrease by 9% from 16.4 to 15.0 mg/week (NS)</li> <li>*1/*3 + *2/*3 + *3/*3: decrease by 10% from 16.4 to 14.7 mg/week (NS)</li> </ul> </li> <li>- VKORC1 TT: <ul style="list-style-type: none"> <li>*1/*2 + *2/*2: decrease by 12% from 11.3 to 10.0 mg/week (NS)</li> <li>*1/*3 + *2/*3 + *3/*3: decrease by 22% from 11.3 to 8.8 mg/week (S)</li> </ul> </li> </ul> </li> <li>- risk of INR &gt; 6 compared to *1/*1: <ul style="list-style-type: none"> <li>- *1/*2 + *1/*3 + *2/*2 + *2/*3 + *3/*3: HR = 3.02 (95% CI 1.62-6.56)</li> <li>- *1/*2 + *2/*2: HR = 3.37 (95% CI 1.68-6.75) for all patients; not significantly elevated for the patients who were not using NSAIDs or antibiotics</li> <li>- *1/*3 + *2/*3 + *3/*3: not significantly elevated for all patients; HR = 3.46 (S) for the patients who were not using</li> </ul> </li> </ul>	<p>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, whereas delayed stabilization is mainly associated with the CYP2C9 genotype." "In this study, we only found an association between being a carrier of the CYP2C9*2 allele and a decreased chance to achieve stability compared with CYP2C9*1/*1 subjects. This indicates that the process of finding the right dose require-</p>

<p><b>ref. 14, continuation</b></p>	<p>*3/*3: D</p>	<p>NSAIDs or antibiotics</p> <ul style="list-style-type: none"> <li>- no significant interaction between VKORC1 and CYP2C9 genotypes</li> <li>- INR &gt; 6 occurred in the period from 0-15 weeks after starting treatment</li> <li>- the time required to achieve stability compared to *1/*1: <ul style="list-style-type: none"> <li>- *1/*2 + *2/*2: HR = 0.61 (95% CI 0.43-0.86).</li> </ul> </li> <li>Also a significant difference for *1/*2 + *2/*2 + *2/*3 versus *1/*1.</li> <li>- *1/*3 + *2/*3 + *3/*3: no difference</li> <li>- no significant interaction between VKORC1 and CYP2C9 genotypes</li> </ul> <p>NOTE: A larger proportion of the difference in required dose is explained by VKORC1 genotype than by CYP2C9 genotype (28.7% and 7.2% respectively).</p> <p>NOTE: The same study population and the same study as in the article by Schalekamp T et al., 2004, but now also with determination of VKORC1.</p>	<p>ment is most difficult in CYP2C9*2 carriers."</p>
<p><b>ref. 15</b> Bohrer T et al. Left ventricular non-compaction associated with a genetic variant of the CYP2C9 gene. Heart Lung Circ 2006;15:269-71.</p>	<p>2 *1/*2: D</p>	<p>Patient had INR &gt; 8 following phenprocoumon 6 mg. The patient was found to be *1/*2. VKORC1 was not determined.</p>	
<p><b>ref. 16</b> zu Schwabedissen CM et al. Obesity is associated with a slower response to initial phenprocoumon therapy whereas CYP2C9 genotypes are not. Eur J Clin Pharmacol 2006;62:713-20.</p>	<p>3 *1/*2: AA *1/*3: AA *2/*2: AA *2/*3: AA</p>	<p>A total of 260 patients, 179x *1/*1, 45x *1/*2, 5x *2/*2, 25x *1/*3, 6x *2/*3, no correction for co-medication;</p> <ul style="list-style-type: none"> <li>- No significant correlation between the CYP2C9 genotype and the dose of phenprocoumon during the initiation phase or the maintenance phase.</li> </ul>	<p>Authors' conclusion: "One major result of the study was that the tested genetic polymorphisms of CYP2C9 affected neither the initial nor the required maintenance doses of phenprocoumon."</p>
<p><b>ref. 17</b> Visser LE et al. Allelic variants of cytochrome P450 2C9 modify the interaction between nonsteroidal anti-inflammatory drugs and coumarin anti-coagulants. Clin Pharmacol Ther 2005;77:479-85.</p>	<p>3 *1/*2: AA *1/*3: AA *2/*2: AA *2/*3: AA  *1/*2 + *1/*3 + *2/*2 + *2/*3: D</p>	<p>A total of 973 patients, 668x *1/*1, 205x *1/*2, 20x *2/*2, 63x *1/*3, 17x *2/*3, of whom 148 on phenprocoumon and 825 on acenocoumarol;</p> <ul style="list-style-type: none"> <li>- *1/*2: decrease in the maintenance dose compared to *1/*1 from 16.7 to 15.3 mg/week, RR INR ≥ 6.0 = 1.08</li> <li>- *1/*3: decrease in the maintenance dose compared to *1/*1 from 16.7 to 12.7 mg/week, RR INR ≥ 6.0 = 1.46</li> <li>- *2/*2: decrease in the maintenance dose compared to *1/*1 from 16.7 to 14.5 mg/week, RR INR ≥ 6.0 = 0.98</li> <li>- *2/*3: decrease in the maintenance dose compared to *1/*1 from 16.7 to 13.7 mg/week, RR INR ≥ 6.0 = 1.46</li> </ul> <p>The RR of an INR ≥ 6.0 was not significantly elevated for any of the genotypes compared to *1/*1. RR is lower for phenprocoumon than for acenocoumarol (0.60 versus 1.00). The INR was ≥ 6.0 for 415 patients.</p> <p>NSAIDs increase the risk of an INR ≥ 6 more strongly for patients with a variant allele than for patients with the *1/*1 genotype (OR of 3.78 (95% CI 2.02-7.09) and 1.69 (95% CI 1.05-2.69) respectively). This effect was greater for patients</p>	

<b>ref. 17, continuation</b>		with a *3 allele than for patients with a *2 allele (OR of 10.8 (95% CI 2.57-34.6) and 2.98 (95% CI 1.09-7.02) respectively).	
<b>ref. 18</b> Schalekamp T et al. Effects of cytochrome P450 2C9 polymorphisms on phenprocoumon anticoagulation status. Clin Pharmacol Ther 2004;76:409-17.	3  *1/*2 + *2/*2: D  *1/*3 + *2/*3 + *3/*3: D	A total of 284 patients, 186x *1/*1, 56x *1/*2, 29x *1/*3, 5x *2/*2, 6x *2/*3 and 2x *3/*3 (of whom 160x *1/*1, 40x *1/*2, 23x *1/*3, 4x *2/*2, 5x *2/*3, and 2x *3/*3 with known dose), mean follow-up was 152 days, target INR was 2.0-3.5, no CYP2C9 inhibitors or inducers co-medication;  - *1/*2 or *2/*2: significantly increased risk of severe overanticoagulation (INR > 6.0) (corrected HR 3.09). During the first 45 days of treatment, the risk of an INR > 6.0 is smaller, but still significant (corrected HR 2.56). Significant decrease in the chance of stability (corrected HR 0.61). Decrease in the weekly dose compared to *1/*1 from 17.4 mg/week by 24% to 13.2 for *1/*2, by 25% to 13.1 for *2/*2 (S, on average 3.7 mg/week lower).  - *1/*3 or *2/*3 or *3/*3: significantly increased risk of INR > 6.0 (corrected HR 2.40). The difference is non-significant during the first 45 days of treatment (corrected HR 1.80). Chance of stability differs non-significantly compared to *1/*1. Reduction in weekly dose compared to *1/*1 from 17.4 mg/week by 27% to 12.7 for *1/*3, by 26% to 12.9 for *2/*3 and by 34% to 11.4 for *3/*3 (S, on average 4.4 mg/week lower).  Comment: age explains a larger proportion of the variability in dose than genotype does (16.8% versus 10.3%).	Authors' conclusion: "In conclusion, our study shows that in phenprocoumon users the presence of at least 1 CYP2C9*2 or CYP2C9*3 allele is associated with an increased risk of severe overanticoagulation and a lower maintenance dosage. CYP2C9*2 carriers have a lower chance to achieve a first period of stability within a period of 6 months after the start of phenprocoumon therapy."  Maintenance dose versus *1/*1: *1/*2: 76% *1/*3: 73% *2/*2: 75% *2/*3: 74% *3/*3: 66%
<b>ref. 19</b> Ufer M et al. Genetic polymorphisms of cytochrome P450 2C9 causing reduced phenprocoumon (S)-7-hydroxylation in vitro and in vivo. Xenobiotica 2004;34:847-59.	3  *1/*2 + *1/*3:A  *2/*2 + *2/*3 + *3/*3: A	A total of 23 healthy volunteers, 4x *1/*1, 4x *1/*2, 3x *2/*2, 5x *1/*3, 4x *2/*3, 3x *3/*3, single dose of 12 mg phenprocoumon;  - S-phenprocoumon: increase in AUC ratio S-phenprocoumon/S-metabolite with increasing number of variant alleles (significant trend). For *3/*3, the metabolic ratios compared to *1/*1 are 2.5x (4' hydroxylation), 5x (6' hydroxylation) and 10x (7' hydroxylation) higher respectively.  - R-phenprocoumon: there is a significant trend between the ratio AUC R-phenprocoumon/R-metabolite and the number of variant alleles only for 7' hydroxylation.  NOTE: The same study population and the same study as Kirchheiner et al., 2004.	Authors' conclusion: "CYP2C9*2 and *3 polymorphisms are associated with a markedly compromised (S)-7-hydroxylation of phenprocoumon <i>in vitro</i> and <i>in vivo</i> . However, other pathways, such as the (S)-4-hydroxylation, remain virtually unaffected by CYP2C9 genotype and may serve as alternative routes of metabolism in individuals with low CYP2C9 activity."
<b>ref. 20</b> Visser LE et al. The risk of bleeding complications in patients with cytochrome P450 CYP2C9*2 or CYP2C9*3 alleles on aceno-	4	A total of 996 patients, of whom 841 on acenocoumarol and 155 on phenprocoumon, 685x *1/*1, 311x variant genotype (210x *1/*2, 63x *1/*3, 23x *2/*2, 15x *2/*3), mean follow-up 481 days after start of VKA;  <u>For both VKAs combined:</u>  - variant genotype: no increased risk of major and minor bleeding during the first 90 days. Risk of major bleeding is	Authors' conclusion: "In our study, CYP2C9 genotype was not associated with a higher rate of bleeding events during the first 90

<p>coumarol or phenprocoumon. Thromb Haemost 2004;92:61-6.</p> <p><b>ref. 20, continuation</b></p>	<p>*1/*2 + *1/*3 + *2/*2 + *2/*3: AA</p>	<p>significantly increased after 460 days.</p> <ul style="list-style-type: none"> <li>- *1/*2 or *2/*2: HR for major + minor, minor, major bleeding was 1.11 (NS), 1.02 (NS) and 1.60 (NS) respectively.</li> <li>- *1/*3 or *2/*3: HR for major + minor, minor, major bleeding was 0.69 (NS), 0.49 (S) and 1.69 (NS) respectively.</li> </ul> <p><u>For phenprocoumon:</u></p> <ul style="list-style-type: none"> <li>- variant genotype: HR major + minor bleeding is 0.81 (NS), HR minor bleeding is 0.76 (NS). The number of events is too low to calculate in the case of major bleeding.</li> </ul>	<p>days of therapy. The higher risk in patients with variant alleles on acenocoumarol was only found for major and fatal bleeding events but not for minor events."</p>
<p><b>ref. 21</b> Visser LE et al. The risk of over-anticoagulation in patients with cytochrome P450 CYP-2C9*2 or CYP2C9*3 alleles on acenocoumarol or phenprocoumon. Pharmacogenetics 2004;14:27-33.</p>	<p>3</p> <p>*1/*2: AA *1/*3: AA *2/*2: AA *2/*3: AA</p>	<p>A total of 1124 patients, 771x *1/*1, 239x *1/*2, 73x *1/*3, 23x *2/*2, 18x *2/*3, with 204 phenprocoumon users, average follow-up 1.8 years, CYP2C9 inhibitors as co-medication;</p> <p><u>With and without co-medication:</u> <b>lower</b> INR after initial dose for variant genotypes, significant for *2/*3. No difference in INR compared to *1/*1 after second dose. No difference in INR during first 6 weeks, 33x INR ≥ 6.0, 24% of these experienced bleeding. No increased risk of over anticoagulation for variant genotypes.</p> <p><u>Without co-medication (173x):</u> No significant decrease in the dose compared to *1/*1:</p> <ul style="list-style-type: none"> <li>- *1/*2: from 15.6 to 14.0 mg/week</li> <li>- *1/*3: from 15.6 to 12.9 mg/week</li> <li>- *2/*2: from 15.6 to 10.0 mg/week</li> <li>- *2/*3: from 15.6 to 16.7 mg/week</li> </ul>	
<p><b>ref. 22</b> Kirchheiner J et al. Effects of CYP2C9 polymorphisms on the pharmacokinetics of R- and S-phenprocoumon in healthy volunteers. Pharmacogenetics 2004;14:19-26.</p>	<p>3</p> <p>*1/*2 + *1/*3: A  *2/*2 + *2/*3 + *3/*3: A</p>	<p>A total of 23 healthy volunteers, 4x *1/*1, 4x *1/*2, 3x *2/*2, 5x *1/*3, 4x *2/*3, 3x *3/*3, single dose of 12 mg phenprocoumon, co-medication unknown;</p> <p>No significant difference in AUC, Cl<sub>or</sub> and t<sub>1/2</sub> between the 6 genotype groups for either R-phenprocoumon or S-phenprocoumon. For Cl<sub>or</sub> and Cl<sub>tot</sub> the ratio S-/R-phenprocoumon decreases significantly with the number of *2 and *3 alleles.</p> <p>Comment: the same study population and the same study as Ufer et al., 2004.</p>	
<p><b>ref. 23</b> Hummers-Pradier E et al. Determination of bleeding risk using genetic markers in patients taking phenprocoumon. Eur J Clin Pharmacol 2003;59:213-9.</p>	<p>3</p> <p>*1/*2: AA  *1/*3: C *2/*3: C</p>	<p>A total of 185 patients of whom 179 were genotyped, 132x *1/*1, 32x *1/*2, 14x *1/*3, 1x *2/*3, mean treatment duration was 5 years.</p> <ul style="list-style-type: none"> <li>- *1/*2: no increased risk of bleeding, <b>increased</b> dose compared to *1/*1 by 5% from 15.29 to 16.02 mg/week (NS).</li> <li>- *1/*3 + *2/*3: significantly increased risk of bleeding, corrected OR 3.64 (4 of the 10 patients with *3 on phenprocoumon experience bleeding), decreased dose for *1/*3 compared to *1/*1 by 13% from 15.29 to 13.29 mg/week (NS), no dose information for the *2/*3 patient.</li> </ul>	<p>Authors' conclusion: "CYP2C9*3 variants are associated with an increased bleeding risk in patients anticoagulated with phenprocoumon."</p> <p>Maintenance dose versus *1/*1: *1/*2: 105% *1/*3: 87%</p>

Risk group	polymorphism for VKORC1, use of CYP2C9 inhibitors
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**Comments:**

- After 2010, studies that only looked at an association with the maintenance dose, but in which the maintenance dose was not determined per genotype or genotype group (for example, genome-wide association or case-control studies) and cases that were identified based only on the INR were not included

in the risk analysis. The reason is that these articles do not provide enough additional information. The article of Just 2021 (Just KS et al. Individualized versus standardized risk assessment in patients at high risk for adverse drug reactions (the IDrug randomized controlled trial)-Never change a running system? Pharmaceuticals (Basel) 2021;14:1056.PMID: 34681280) was not included in the risk analysis, because genetic information was only one of the five risk factors individualized in this study (next to bleeding- and thromboembolic-risk-scores, potential drug-drug-interactions, age, and renal function) and even the one mentioned last. As a result, this study was only partially genotype-guided. In addition, only patients treated for at least 3 months were included in the study and the vast majority of patients provided more retrospective data than the required 3 months. This means that therapy was already established in the majority of patients at study entry (maintenance phase). Finally, it was at the discretion of the general practitioner in which way and to what extent he used the provided information for further treatment. Therefore, it is not sure whether and to which extent the information on CYP2C9 genotype was used for treatment. This is especially true because the study refers to the KNMP Pharmacogenetic Working Group for the CYP2C9-phenprocoumon interaction, which did not recommend adjustment of therapy for patients with a CYP2C9-variant at that time.

- **Cost-effectiveness:**

- o Verhoef TI et al. Cost-effectiveness of pharmacogenetic-guided dosing of phenprocoumon in atrial fibrillation. Pharmacogenomics 2013;14:869-83. PMID: 23746182.

In patients who start using phenprocoumon at the age of 71.5 years, genotyping yields acceptable or excessively high costs per Quality Adjusted Life-Year (QALY), depending on the scenario that is selected. Compared to the current standard treatment, genotyping before start of treatment costs € 15.15 more and the increase in QALYs was 0.0057 (2 days in good health).

The calculation was based on genotyping costs of € 40 and costs per INR measurement of € 11.74. Most of the information in the model was obtained from literature, whilst an assumption was only made for the following points: the risk of a stroke or TIA if a thromboembolism occurs, the number of INR measurements during the first month and the number of extra INR measurements after bleeding or thromboembolism.

Cost-effectiveness was defined as less than € 20,000 per QALY gained.

A best-case and worst-case scenario were worked out with the costs of genotyping (€ 20 to € 160) and effectiveness of genotyping (50% more than assumed and 50% less than assumed) as the variables. In 95% of the cases, the genotype-based treatment is more expensive and more effective. In 4.7% of the cases, the genotype-based treatment is dominant (more effective and cheaper). A total of 75.6% of the scenarios were cost-effective (costs of 1 QALY less than € 20,000). Due to the many uncertainties in the model, it is still too soon to conclude whether patients should be genotyped before starting treatment with phenprocoumon.

- **Dose algorithms:**

- o van Schie RM et al. Loading and maintenance dose algorithms for phenprocoumon and acenocoumarol using patient characteristics and pharmacogenetic data. Eur Heart J 2011; 32:1909-1917.

An algorithm for the maintenance dose of phenprocoumon was developed based on data from 559 phenprocoumon users with an INR target of 2.0-3.5. The algorithm was validated in an independent data set of 229 phenprocoumon users, of whom the parameters of height and weight 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 can be calculated based on the calculated maintenance dose using the formula mentioned below. The algorithm explained 55.9% of the variation in dose requirement, with the CYP2C9 polymorphism being responsible for 4.6% of the variation. The mean absolute error in the calculated maintenance dose was 0.45 mg/day. These figures 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 will result in improved initiation and safety of phenprocoumon treatment.

The algorithm found in the study was:

$$\sqrt{\text{(mean maintenance dose (mg/week))}} = 2.874 - 0 \text{ (if CYP2C9*1/*1)} - 0.259 \text{ (if CYP2C9*1/*2)} - 0.342 \text{ (if CYP2C9*1/*3)} - 0.447 \text{ (if CYP2C9*2/*2)} - 0.684 \text{ (if CYP2C9*2/*3)} - 0.681 \text{ (if CYP2C9*3/*3)} - 0 \text{ (if VKORC1 CC)} - 0.601 \text{ (if VKORC1 CT)} - 1.394 \text{ (if VKORC1 TT)} - 0.015 * \text{age (years)} + 0.026 \text{ (if female)} + 0.011 * \text{height (cm)} + 0.008 * \text{body weight (kg)} - 0.345 \text{ (if amiodarone is being used)}$$

Formula for calculation of the loading dose based on the calculated maintenance dose:

$$\text{maintenance dose (mg/day)} = (D_1 * e^{-2k} + D_2 * e^{-k} + D_3) / (1 - e^{-k})$$

with D<sub>1</sub>, D<sub>2</sub> and D<sub>3</sub> being the dose on days 1, 2 and 3 respectively and with the elimination rate constant k being equal to ln(2)/T<sub>1/2</sub>.

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 is chosen so that it results in the lower limit of the indicated maintenance dosage area.

- 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 maintenance dose of phenprocoumon was developed based on data from 75 phenprocoumon users with an INR target of 2.0-3.0. The algorithm was not validated in an independent data set. The algorithm explained 48.6% of the variation in dose requirement. The CYP2C9 polymorphism had no effect on the variability in the dose, but did have an effect on the variation in plasma concentration. The mean absolute error in the calculated maintenance dose was 0.52 mg/day. Passing-Bablok regression analysis demonstrated a good correlation between the actual and calculated phenprocoumon dose (r=0.701).  
The algorithm found in the study was:  
 $\sqrt{\text{maintenance dose (mg/day)}} = 0.460 + 0.238 \text{ (if VKORC1 CC)} - 0.271 \text{ (if VKORC1 TT)} + 0.007 * \text{height (cm)} - 0.004 * \text{age (in years)}$
- 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 maintenance dose of phenprocoumon was developed based on data from 185 phenprocoumon users with an INR target of 2.0-3.0. The algorithm was not validated in an independent data set. The algorithm explained 31% of the variation in dose requirement, with the CYP2C9\*3 polymorphism responsible for 4.7% of the variation.  
 $\sqrt{\text{maintenance dose (mg/week)}} = 4.823 - 0.4148 * \text{the number of VKORC1 T alleles} - 0.0187 * \text{age (in years)} - 0.5535 * \text{the number of CYP2C9 *3 alleles} - 0.2503 * \text{the number of CYP2C9 *2 alleles} + 0.057 * \text{body weight (kg)}$

Date of literature search: 22 July 2025.

	Genotype	Code	Gene-drug interaction	Action	Date
KNMP Pharmacogenetics Working Group decision	*1/*2	4 D	Yes	No	29 September 2025
	*1/*3	4 D	Yes	No	
	*2/*2	4 D	Yes	Yes	
	*2/*3	4 D	Yes	Yes	
	*3/*3	4 D	Yes	Yes	
	IM	3 AA	Yes	No	
	PM	3 AA	Yes	Yes	

#### Mechanism:

Phenprocoumon consists of a racemic mixture. The S-enantiomer is 2-5x more potent than the R-enantiomer for the effect on coagulation.

The S-enantiomer is almost completely metabolised by CYP2C9 via 6' and 7' hydroxylation. The R-enantiomer is mainly metabolised by CYP2C9 and CYP3A4. A proportion of the phenprocoumon is excreted in unchanged form.

#### Clinical Implication Score:

Table 1: Definitions of the available Clinical Implication Scores

<b>Potentially beneficial</b>	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 +
<b>Beneficial</b>	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 +
<b>Essential</b>	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

<b>Clinical Implication Score Criteria</b>	<b>Possible Score</b>	<b>Given Score</b>
<b>Clinical effect associated with gene-drug interaction (drug- or diminished efficacy-induced)</b> <ul style="list-style-type: none"> <li>• CTCAE Grade 3 or 4 (clinical effect score D or E)</li> <li>• CTCAE Grade 5 (clinical effect score F)</li> </ul>	+ ++	+
<b>Level of evidence supporting the associated clinical effect grade <math>\geq 3</math></b> <ul style="list-style-type: none"> <li>• One study with level of evidence score <math>\geq 3</math></li> <li>• Two studies with level of evidence score <math>\geq 3</math></li> <li>• Three or more studies with level of evidence score <math>\geq 3</math></li> </ul>	+ ++ +++	
<b>Number needed to genotype (NNG) in the Dutch population to prevent one clinical effect grade <math>\geq 3</math></b> <ul style="list-style-type: none"> <li>• <math>100 &lt; \text{NNG} \leq 1000</math></li> <li>• <math>10 &lt; \text{NNG} \leq 100</math></li> <li>• <math>\text{NNG} \leq 10</math></li> </ul>	+ ++ +++	
<b>PGx information in the Summary of Product Characteristics (SmPC)</b> <ul style="list-style-type: none"> <li>• At least one genotype/phenotype mentioned</li> </ul> OR <ul style="list-style-type: none"> <li>• Recommendation to genotype</li> </ul> OR <ul style="list-style-type: none"> <li>• At least one genotype/phenotype mentioned as a contra-indication in the corresponding section</li> </ul>	+ ++ ++	
<b>Total Score:</b>	10+	1+
<b>Corresponding Clinical Implication Score:</b>		Potentially beneficial