# CYP2C9: phenprocoumon 1870 to 1876

*2 = CYP2C9 gene variant with decreased activity, *3 = CYP2C9 gene variant with strongly decreased activity, $Cl_{or}$ = oral clearance, EM = extensive metaboliser (*1/*1) (normal CYP2C9 enzyme activity), HR = hazard ratio, IM = 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, NS = non-significant, PM = poor metaboliser, other genotype (strongly decreased CYP2C9 enzyme activity involving one or two gene variants with decreased activity other than *2 or *3), RR = relative risk, S = significant, 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 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 the 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. 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. As a result, there is insufficient evidence to recommend an adjustment of the initial dose, frequency of the INR monitoring or choice of the medicine. The risk of bleeding is not strongly elevated for patients with a variant allele, possibly because of the relatively small effect and because of the INR being regularly monitored in all patients. The Dutch Pharmacogenetics Working Group therefore decides that no action is required (yes/no-interactions).
<u>Initial dose</u>
Verhoef 2013 found no significant differences in adverse events, thromboembolism and underanticoagulation or over-anticoagulation between treatment using a genotype-based algorithm and an algorithm without genotype. There is a strong trend towards an increase in the time that the INR was in the therapeutic range only during the first 4 weeks, but Baranova 2017 suggested patients without a CYP2C9 or VKORC1 variant to be responsible for this. Zhang 2017 found a positive effect of the genotype-based algorithm on the time that the INR was in and above the therapeutic range for patients < 75 years, but a negative effect for patients ≥ 75 years. In addition, their data suggest patients with two or more variants of CYP2C9 and/or VKORC1 to be responsible for this. However, they did not investigate whether the better INR results for patients < 75 years also resulted in better clinical outcomes and whether both CYP2C9 and VKORC1 variants contributed to the better INR results. For this reason, there is insufficient evidence to support an adjustment of the initial dose for both patients ≥ 75 years and patients < 75 years.
<u>Choice of medicine</u>
With regard to bleeding, the article by Visser 2004 that relates to the Netherlands found a fairly small difference. In addition, for the 155 phenprocoumon patients alone, the study did not find a significantly increased bleeding risk. The higher risk of bleeding for patients with CYP2C9 polymorphisms is not unacceptable and does not justify withholding anticoagulant therapy or switching to direct-acting oral anticoagulant therapy. Whereas all direct-acting oral anticoagulants (rivaroxaban, apixaban, dabigatran and edoxaban) are authorised for the treatment of venous thromboembolism, the prevention of recurrent venous thromboembolism and the prevention of venous thromboembolism in patients with atrial fibrillation, only rivaroxaban, apixaban and dabigatran are authorised for the prevention of thromboembolism in patients undergoing hip or knee replacement surgery. In addition, none of the direct-acting oral anticoagulants is authorised for use in patients with heart valve abnormalities.
Non-consistent results were found in studies outside the Netherlands. Hummers-Pradier 2003 with 179 patients found CYP2C9 *3 to increase the risk of bleeding, but Brehm 2016 with 63 patients and Brehm 2013 with 175 patients did not find an effect of CYP2C9 variants on bleeding risk.
<u>Frequency of the INR monitoring</u>
Advising the National INR Monitoring Service (trombosedienst) to modify the frequency of INR monitoring is not useful: if the INR is not stable, they always measure more frequently. If patients are started on treatment in a hospital,

the monitoring is often performed by residents or internists. In this case too there is insufficient evidence to support the benefit of recommending more frequent monitoring for patients with a variant allele. One article found a longer time required to achieve a stable INR for a proportion of the patients with a variant allele. However, another article found that the time was shorter.
Visser 2005 found that NSAIDs increase the risk of an INR ≥ 6 in patients with a variant allele more strongly than in patients without a variant allele. However, the relevant study used 85% acenocoumarol and only 15% phenprocoumon. Moreover, there is no study that confirms this effect for phenprocoumon. This means that there is insufficient evidence to warrant passing the CYP2C9 genotypes on to the National INR Monitoring Service (trombosedienst) for extra monitoring of the INR during NSAID use.
Overview of kinetic and clinical effects
You can find a detailed overview of the observed kinetic and clinical effects 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.

<table>
<tr><th>Source</th><th>Code</th><th>Effect</th><th>Comments</th></tr>
<tr><td>ref. 1<br>Zhang Y et al. Age-stratified outcome of a genotype-guided dosing algorithm for acenocoumarol and phenprocoumon.<br>J Thromb Haemost 2017;15:454-464.<br>PubMed PMID: 27992949.</td><td>3</td><td>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 control 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).<br>All INRs were measured during the first 12 weeks of treatment.<br>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).<br>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.<br>Differences in percentages of time in or outside the therapeutic range were adjusted for height, weight, sex, enzyme inhibitors, and enzyme inducers.<br><br>Genotyping:<br>- 107x *1/*1<br>- 27x *1/*2<br>- 18x *1/*3<br>- 4x *2/*2<br>- 2x *2/*3<br>- 1x genotype unknown (clinical algorithm, < 75 years)<br><br>Results:<br>
<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="3">% 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>
</table>
</td><td>Author’s conclusion:<br>”The results support the use of genotype-guided dosing for phenprocoumon in patients < 75 years. For patients ≥ 75 years the phenprocoumon algorithm should be revised and further tested.”</td></tr>
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| **ref. 1, continuation** | geno-type-guided versus not ge-notype-guided therapy, patients < 75 years: AA# | | ≥ 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 group) | 55.6% | |
| | | | < 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). | | | |
| | | % of time with a suprathe-rapeutic 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% | |
| | geno-type-guided versus not ge-notype-guided therapy, patients ≥ 75 years: A | | ≥ 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% | |

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|---|---|---|---|---|---|---|
| **ref. 1, continuation** | | | | ≥ 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 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. | | | |

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<td>ref. 2<br>Brehm K et al.<br>Genetic variations of phenprocoumon metabolism in patients with ventricular assist devices.<br>Eur J Cardiothorac Surg<br>2016;50:275-80.<br>PubMed PMID:<br>26984978.</td>
<td>3<br><br>(*1/*3+<br>*2/*3+<br>*3/*3):<br>AA<br><br>(*1/*2+<br>*2/*2+<br>*2/*3):<br>AA</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.<br>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.<br>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.<br>High complication (major bleeding or thromboembolism) rates were observed particularly in the early post-operative period. Relevant co-medication was not excluded.<br>The influence of genotypes on the occurrence of adverse events was evaluated by univariate logistic regression analysis.<br><br>Genotyping:<br>- 39x *1/*1<br>- 13x *1/*2<br>- 8x *1/*3<br>- 1x *2/*2<br>- 1x *2/*3<br>- 1x *3/*3<br><br>Results:
<table>
<tr><td colspan="3">Results compared to *1/*1:</td></tr>
<tr><td></td><td>*2-allele</td><td>*3-allele</td></tr>
<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>
</table>
Note: Genotyping was for *2 and *3. These are the most important gene variants in this German population.</td>
<td>Author’s conclusion:<br>”CYP2C9 polymorphisms showed no effect on phenprocoumon doses.”</td>
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<td>ref. 3<br>Verhoef TI et al.<br>A randomized trial of genotype-guided dosing of acenocoumarol and phenprocoumon.<br>N Engl J Med<br>2013;369:2304-12.<br>PubMed PMID:<br>24251360.</td>
<td>3</td>
<td>Patients who had not previously received coumarins 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.<br><br>Genotyping:<br>- 112x *1/*1</td>
<td>Authors’ conclusion:<br>“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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<td>ref. 3, continuation<br><br>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>genotype-guided versus not genotype-guided therapy : AA</td>
<td>- 28x *1/*2<br>- 18x *1/*3<br>- 4x *2/*2<br>- 2x *2/*3<br><br>Genotype-based algorithm compared to clinical algorithm:<br>- no increase in the time that the INR was in the therapeutic range during the entire treatment (NS)<br>- no significant increase in the time that the INR was in the 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)<br>- no difference in the incidence of adverse events and thromboembolism (NS)<br>- 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)<br><br>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:
<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</td><td>NS</td><td>NS</td></tr>
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</td>
<td>Authors' conclusion:<br>'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.<br>EU-PACT genetic-</td>
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| **ref. 3, continuation** | | | variants | | | 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 could lead to a higher benefit of genotyping.' |
| | | % 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 | |
| | | | no CYP2C9 variants and one VKORC1 variant | NS | NS | |
| | | | 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. 4**<br>Abduljalil K et al.<br>Quantifying the effect of covariates | 3 | 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, | | | | Authors' conclusion:<br>"The model confirmed CYP2C9 and |

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| on concentrations and effects of steady-state phenprocoumon using a population pharmacokinetic/pharmacodynamic model.<br>Clin Pharmacokinet 2013;52:359-71.<br>PMID: 23519598.<br><br>**ref. 4, continuation** | <br><br><br><br><br><br><br><br><br>*1/*2: AA<br><br>*1/*3: A<br>*2/*2: AA<br>*2/*3: AA | but no significant effect of CYP2C9 inhibitors/inducers on the clearance.<br><br>Genotyping:<br>- 172x *1/*1<br>- 61x *1/*2<br>- 36x *1/*3<br>- 5x *2/*2<br>- 4x *2/*3<br><br>Maintenance dose versus *1/*1:<br>- *1/*2: decrease by 17% (from 14.74 to 12.30 mg per week) (NS for the sub-group with VKORC1 CC)<br>- *1/*3: decrease by 20% (from 14.74 mg to 11.74 mg per week) (S for the sub-group with VKORC1 CC)<br>- *2/*2: decrease by 32% (from 14.74 mg to 9.95 mg per week) (NS, significance not determined)<br>- *2/*3: decrease by 45% (from 14.74 mg to 8.06 mg per week) (NS, significance not determined)<br><br>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. | 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 or inducers) and presence of atrial fibrillation.” |
| **ref. 5**<br>Brehm K et al.<br>Mechanical heart valve recipients: anticoagulation in patients with genetic variations of phenprocoumon metabolism.<br>Eur J Cardiothorac Surg 2013;44:309-14.<br>PMID:23423913. | 3<br><br><br><br><br><br><br><br>*1/*2: AA<br>*1/*3: AA<br>*2/*2: AA<br>*2/*3: AA | 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.<br><br>Genotyping:<br>- 109x *1/*1<br>- 38x *1/*2<br>- 24x *1/*3<br>- 3x *2/*2<br>- 1x *2/*3<br><br>(genotype with *3) versus (genotype with *2) versus *1/*1:<br>- no difference in the risk of major and minor bleeding (NS)<br>- no difference in the risk of venous thromboembolism (NS)<br><br>*2/*3 versus *2/*2 versus *1/*3 versus *1/*2 versus *1/*1:<br>- no significant decrease in the maintenance dose (10.5 versus 12.0 versus 14.2 versus 16.6 versus 15.8 mg/week) (NS) | Authors’ conclusion:<br>“No influence of CYP2C9 polymorphism on phenprocoumon dosage and anticoagulation-related complications was found.” |
| **ref. 6**<br>Geisen C et al.<br>Prediction of phenprocoumon maintenance dose and phenprocoumon plasma concentration by genetic and non-genetic parameters.<br>Eur J Clin Pharmacol 2011;67:371-81.<br>PMID: 21110013. | 4<br><br><br><br><br><br><br><br>*1/*2: A<br>*1/*3: A<br>*2/*3: A | 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.<br><br>Genotyping:<br>- 48x *1/*1<br>- 18x *1/*2<br>- 8x *1/*3<br>- 1x *2/*3<br><br>*2/*3 versus *1/*3 versus *1/*2 versus *1/*1:<br>- increase in the median plasma concentration of phenprocoumon (5.1 versus 2.00 versus 2.02 versus 1.84 mg/L) (S)<br>- no difference in the median maintenance dose (2.14 versus 2.25 versus 1.71 versus 2.14 mg/day) (NS)<br><br>CYP2C9 genotype is an independent variable for the maintenance dose (multivariable regression analysis), but has a limi- | Authors’ conclusion:<br>“We did not detect an effect of CYP2C9 on phenprocoumon maintenance doses.” |

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| **ref. 6, continuation** | | ted influence. CYP2C9 was not included in the final dose algorithm. | |
| **ref. 7**<br>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. PMID: 21057703. | 3<br><br>(*1/*2 + *1/*3 + *2/*3 + *3/*3): AA[#] | 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.<br><br>Genotyping:<br>Initiation phase: Maintenance therapy:<br>- 28x *1/*1 - 56x *1/*1<br>- 17x *1/*2 - 20x *1/*2<br>- 7x *1/*3 - 11x *1/*3<br>- 1x *2/*3 - 3x *2/*3<br>- 1x *3/*3 - 1x *3/*3<br><br>*Initiation phase:*<br>(*2 or *3) versus *1/*1:<br>- no difference in dose during the initiation phase (NS)<br>- no difference in the first measured INR (NS)<br>- decrease in the time to achieve stable INR by 43% (from 30 to 17 days) (S).<br>The HR for achieving a stable INR at an earlier stage was 1.83 (95% CI: 1.05-3.18).<br>- a 38% decrease in the number of visits to the thrombosis physician required before achieving a stable INR (from 8 to 5) (S)<br>- no difference in the time to the first INR > 3.0 (NS)<br>- no difference in the percentage of the time that INR is > 3.0 (NS)<br><br>*Maintenance therapy:*<br>- no difference in the time that INR is < 2.0 or > 3.0 between (*2 or *3) and *1/*1 (NS) | Authors' conclusion:<br>"Although Schalekamp et al. observed an increased risk of overanticoagulation 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." |
| **ref. 8**<br>Cadamuro J et al. Genetic determinants of acenocoumarol and phenprocoumon maintenance dose requirements. Eur J Clin Pharmacol 2010;66:253-60. | 4<br><br>*1/*2: A<br><br>*1/*3: A<br><br>*2/*2: A<br><br>*2/*3: A | 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;<br><br>Maintenance dose (corrected for age, gender and last INR) versus *1/*1:<br>- *1/*2: decrease by 18% from 15.81 to 12.96 mg/week (S for the trend)<br>- *1/*3: decrease by 21% from 15.81 to 12.45 mg/week (S for the trend)<br>- *2/*2: decrease by 57% from 15.81 to 6.72 mg/week (S for the trend)<br>- *2/*3: decrease by 20% from 15.81 to 12.63 mg/week (S for the trend)<br><br>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. | Authors' conclusion:<br>"These results reveal that interindividual variability in weekly phenprocoumon maintenance dose requirement is mainly dependent on the VKORC1 1173 C>T and the CYP2C9*3 alleles. VKORC1 and CYP2C9 genotyping might provide helpful information to prevent serious bleeding events in subjects receiving phenprocoumon." |
| **ref. 9**<br>Werner D et al. Pharmacogenetic characteristics of patients with | 3 | 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 | Authors' conclusion:<br>"The data suggest a fundamental role |

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| complicated phenprocoumon dosing.<br>Eur J Clin Pharmacol 2009;65:783-8.<br><br>**ref. 9, continuation** | *2/*2 + *2/*3 + *3/*3: A<br><br>*1/*2 + *1/*3: AA | days) (n = 7) or INR unchanged for ≥ 1 week after stopping phenprocoumon (n = 7)), co-medication with an effect on the INR was not excluded;<br><br>Case group versus control group:<br>- percentage of patients with a variant allele is elevated by a factor 1.75 (95% CI 1.17-2.60)<br>- percentage of *2/*2 + *2/*3 + *3/*3 is elevated by a factor 4.0 (95% CI 1.25-12.7)<br>- no significant difference in percentage of *1/*2 + *1/*3 (NS) | of VKORC1 haplotypes and a minor role of CYP2C9 variants in the anticoagulation property of phenprocoumon." |
| **ref. 10**<br>Qazim B et al. Dependency of phenprocoumon dosage on polymorphisms in the VKORC1 and CYP-2C9 genes.<br>J Thromb Thrombolysis 2009;28:211-4. | 3<br><br>*1/*2: AA<br>*1/*3: AA<br>*2/*2: AA | 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;<br><br>- no difference in INR values between the various genotypes<br>- maintenance dose versus *1/*1:<br>- *1/*2: decrease by 24% from 13.5 to 10.2 mg/week (NS)<br>- *1/*3: decrease by 46% from 13.5 to 7.3 mg/week (NS)<br>- *2/*2: decrease by 61% from 13.5 to 5.3 mg/week (NS) | Authors' conclusion:<br>"Though VKORC1 and CYP2C9 polymorphisms influence the phenprocoumon dosage necessary to achieve therapeutic anticoagulation, anticoagulation is therapeutic if carefully monitored." |
| **ref. 11**<br>Schalekamp T et al. VKORC1 and CYP-2C9 genotypes and phenprocoumon anticoagulation status: interaction between both genotypes affects dose requirement.<br>Clin Pharmacol Ther 2007;81:185-93. | 4<br><br>*1/*2 + *2/*2: D<br><br>*1/*3 + *2/*3 + *3/*3: D | 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;<br>Doses were corrected for heart failure, gender and age. The risk of INR > 6 was also corrected for the VKORC1 genotype.<br><br>- VKORC1 has a significant effect on the dose reduction by CYP2C9 polymorphisms.<br>Maintenance dose versus *1/*1:<br>- VKORC1 CC:<br>*1/*2 + *2/*2: decrease by 28% from 22.4 to 16.2 mg/week (S)<br>*1/*3 + *2/*3 + *3/*3: decrease by 28% from 22.4 to 16.1 mg/week (S)<br>- VKORC1 CT:<br>*1/*2 + *2/*2: decrease by 9% from 16.4 to 15.0 mg/week (NS)<br>*1/*3 + *2/*3 + *3/*3: decrease by 10% from 16.4 to 14.7 mg/week (NS)<br>- VKORC1 TT:<br>*1/*2 + *2/*2: decrease by 12% from 11.3 to 10.0 mg/week (NS)<br>*1/*3 + *2/*3 + *3/*3: decrease by 22% from 11.3 to 8.8 mg/week (S)<br>- risk of INR > 6 compared to *1/*1:<br>- *1/*2 + *1/*3 + *2/*2 + *2/*3 + *3/*3: HR = 3.02 (95% CI 1.62-6.56)<br>- *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<br>- *1/*3 + *2/*3 + *3/*3: not significantly elevated for all patients; HR = 3.46 (S) for the patients who were not using NSAIDs or antibiotics<br>- no significant interaction between VKORC1 and CYP-2C9 genotypes | Authors' conclusion:<br>"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 CYP-2C9 genotype."<br>"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 requirement is most difficult in CYP2C9*2 carriers." |

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| **ref. 11, continuation** | | - INR > 6 occurred in the period from 0-15 weeks after starting treatment<br>- the time required to achieve stability compared to *1/*1:<br>- *1/*2 + *2/*2: HR = 0.61 (95% CI 0.43-0.86). Also a significant difference for *1/*2 + *2/*2 + *2/*3 versus *1/*1.<br>- *1/*3 + *2/*3 + *3/*3: no difference<br>- no significant interaction between VKORC1 and CYP-2C9 genotypes<br><br>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).<br>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. | |
| **ref. 12**<br>Bohrer T et al.<br>Left ventricular non-compaction associated with a genetic variant of the CYP-2C9 gene.<br>Heart Lung Circ 2006;15:269-71. | 2<br>*1/*2: D | Patient had INR > 8 following phenprocoumon 6 mg. The patient was found to be *1/*2.<br>VKORC1 was not determined. | |
| **ref. 13**<br>zu Schwabedissen CM et al.<br>Obesity is associated with a slower response to initial phenprocoumon therapy whereas CYP2C9 genotypes are not.<br>Eur J Clin Pharmacol 2006;62:713-20. | 3<br><br>*1/*2: AA<br>*1/*3: AA<br>*2/*2: AA<br>*2/*3: AA | 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;<br><br>- No significant correlation between the CYP2C9 genotype and the dose of phenprocoumon during the initiation phase or the maintenance phase. | Authors' conclusion:<br>"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." |
| **ref. 14**<br>Visser LE et al.<br>Allelic variants of cytochrome P450 2C9 modify the interaction between nonsteroidal anti-inflammatory drugs and coumarin anticoagulants.<br>Clin Pharmacol Ther 2005;77:479-85. | 3<br><br>*1/*2: AA<br>*1/*3: AA<br>*2/*2: AA<br>*2/*3: AA<br><br>*1/*2 + *1/*3 + *2/*2 + *2/*3: D | 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;<br><br>- *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<br>- *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<br>- *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<br>- *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<br>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.<br>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 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). | |
| **ref. 15**<br>Schalekamp T et al. | 3 | A total of 284 patients, 186x *1/*1, 56x *1/*2, 29x *1/*3, 5x *2/*2, 6x *2/*3 and 2x *3/*3, mean follow-up was 152 days, | Authors' conclusion: |

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| Effects of cytochrome P450 2C9 polymorphisms on phenprocoumon anticoagulation status. Clin Pharmacol Ther 2004;76:409-17.<br><br>**ref. 15, continuation** | *1/*2 + *2/*2: D<br><br>*1/*3 + *2/*3 + *3/*3: D | target INR was 2.0-3.5, no CYP2C9 inhibitors or inducers co-medication;<br><br>- *1/*2 or *2/*2: significantly increased risk of severe over-anticoagulation (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 to 13.1 mg/week (S, 3.7 mg).<br>- *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 to 12.7 for *1/*3, 12.9 for *2/*3 and 11.4 for *3/*3 (S, on average 4.4 mg/week lower).<br><br>Comment: age explains a larger proportion of the variability in dose than genotype does (16.8% versus 10.3%). | "In conclusion, our study shows that in phenprocoumon users the presence of at least 1 CYP-2C9*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." |
| **ref. 16**<br>Ufer M et al.<br>Genetic polymorphisms of cytochrome P450 2C9 causing reduced phenprocoumon (S)-7-hydroxylation in vitro and in vivo. Xenobiotica 2004;34:847-59. | 3<br><br>*1/*2 + *1/*3:A<br><br>*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;<br><br>- 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.<br>- 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.<br><br>NOTE: The same study population and the same study as Kirchheiner et al., 2004. | Authors' conclusion:<br>"CYP2C9*2 and *3 polymorphisms are associated with a markedly compromised (S)-7-hydroxylation of phenprocoumon *in vitro* and *in vivo.* 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." |
| **ref. 17**<br>Visser LE et al.<br>The risk of bleeding complications in patients with cytochrome P450 CYP-2C9*2 or CYP2C9 *3 alleles on acenocoumarol or phenprocoumon. Thromb Haemost 2004;92:61-6. | 4<br><br>*1/*2 + *1/*3 + *2/*2 + *2/*3: F | 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 coumarin;<br><br><u>For both coumarins combined:</u><br>- variant genotype: no increased risk of major and minor bleeding during the first 90 days. Risk of major bleeding is significantly increased after 460 days.<br>- *1/*2 or *2/*2: HR for major + minor, minor, major bleeding was 1.11 (NS), 1.02 (NS) and 1.60 (NS) respectively.<br>- *1/*3 or *2/*3: HR for major + minor, minor, major bleeding was 0.69 (NS), 0.49 (S) and 1.69 (NS) respectively.<br><br><u>For phenprocoumon:</u><br>- 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. | Authors' conclusion:<br>"In our study, CYP-2C9 genotype was not associated with a higher rate of bleeding events during the first 90 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." |

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| **ref. 18**<br>Visser LE et al.<br>The risk of over-anticoagulation in patients with cytochrome P450 CYP-2C9*2 or CYP2C9*3 alleles on acenocoumarol or phenprocoumon.<br>Pharmacogenetics 2004;14:27-33. | 3<br><br>*1/*2: AA<br>*1/*3: AA<br>*2/*2: AA<br>*2/*3: AA | 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;<br><br>With **and** without co-medication:<br>**lower** 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.<br><br>Without co-medication (173x):<br>No significant decrease in the dose compared to *1/*1:<br>- *1/*2: from 15.6 to 14.0 mg/week<br>- *1/*3: from 15.6 to 12.9 mg/week<br>- *2/*2: from 15.6 to 10.0 mg/week<br>- *2/*3: from 15.6 to 16.7 mg/week | |
| **ref. 19**<br>Kirchheiner J et al.<br>Effects of CYP2C9 polymorphisms on the pharmacokinetics of R- and S-phenprocoumon in healthy volunteers.<br>Pharmacogenetics 2004;14:19-26. | 3<br><br>*1/*2 + *1/*3: A<br><br>*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, co-medication unknown;<br><br>No significant difference in AUC, $Cl_{or}$ and t½ between the 6 genotype groups for either R-phenprocoumon or S-phenprocoumon. For $Cl_{or}$ and $Cl_{tot}$ the ratio S-/R-phenprocoumon decreases significantly with the number of *2 and *3 alleles.<br><br>Comment: the same study population and the same study as Ufer et al., 2004. | |
| **ref. 20**<br>Hummers-Pradier E et al.<br>Determination of bleeding risk using genetic markers in patients taking phenprocoumon.<br>Eur J Clin Pharmacol 2003;59:213-9. | 3<br><br>*1/*2: A<br><br>*1/*3: C<br>*2/*3: C | 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.<br><br>- *1/*2: no increased risk of bleeding, **increased** dose compared to *1/*1 from 15.29 to 16.02 mg/week (NS).<br>- *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 compared to *1/*1 from 15.29 to 13.29 mg/week (NS). | Authors' conclusion:<br>"CYP2C9*3 variants are associated with an increased bleeding risk in patients anticoagulated with phenprocoumon." |

AA#: There is a significant effect, but this effect is positive rather than negative.

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| Risk group | polymorphism for VKORC1, use of CYP2C9 inhibitors |

**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 status report. The reason is that these articles do not provide enough additional information.
- **Cost-effectiveness:**
    - 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:**
  - 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:
    √ (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 CC) – 0.601 (if VKORC1 CT) – 1.394 (if VKORC1 TT) – 0.015 * age (years) + 0.026 (if female) + 0.011 * height (cm) + 0.008 * body weight (kg) – 0.345 (if amiodarone is being used)
    Formula for calculation of the loading dose based on the calculated maintenance dose:
    maintenance dose (mg/day) = $(D_1*e^{-2k} + D_2*e^{-k} + D_3)/(1-e^{-k})$
    with $D_1$, $D_2$ and $D_3$ being the dose on days 1, 2 and 3 respectively and with the elimination rate constant k being 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 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:
    √ (maintenance dose (mg/day)) = 0.460 + 0.238 (if VKORC1 CC) – 0.271 (if VKORC1 TT) + 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 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.
√ (maintenance dose (mg/week)) = 4.823 – 0.4148 * the number of VKORC1 T 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: 13 February 2018

| | Genotype | Code | Gene-drug interaction | Action | Date |
|---|---|---|---|---|---|
| Dutch Pharmacogenetics Working Group decision | *1/*2 | 4 F | Yes | No | 14 May 2018 |
| | *1/*3 | 4 F | Yes | No | |
| | *2/*2 | 4 F | Yes | No | |
| | *2/*3 | 4 F | Yes | No | |
| | *3/*3 | 4 D | Yes | No | |
| | IM | 4 F | Yes | No | |
| | PM | 4 F | Yes | No | |

**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.
A genetic polymorphism for CYP2C9 results in a decreased metabolic capacity of the enzyme, resulting in a possible increase in the plasma concentration of S-phenprocoumon and - to a lesser extent - R-phenprocoumon.