# Economic evaluation of a pharmacogenetic dosing algorithm for coumarin anticoagulants in The Netherlands

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**Abstract**

*Aims:* to investigate the cost-effectiveness of a pharmacogenetic dosing algorithm versus a clinical dosing algorithm for coumarin anticoagulants in The Netherlands.

*Materials & methods:* A decision-analytic Markov model was used to analyze the cost-effectiveness of pharmacogenetic dosing of phenprocoumon and acenocoumarol versus clinical dosing.

*Results:* Pharmacogenetic dosing increased costs by €33 and QALYs by 0.001. The incremental cost-effectiveness ratios (ICERs) were €28,349 and €24,427 per QALY gained for phenprocoumon and acenocoumarol respectively. At a willingness to pay threshold of €20,000 per QALY, the pharmacogenetic dosing algorithm was not likely to be cost-effective compared to the clinical dosing algorithm.

*Conclusions:* Pharmacogenetic dosing improves health only slightly when compared with clinical dosing. However, availability of low-cost genotyping would make it a cost-effective option.

**Keywords**

**Introduction**

Many observational studies have investigated the pharmacogenetics of coumarin anticoagulants such as warfarin, acenocoumarol and phenprocoumon [1-4]. These drugs are frequently prescribed for patients with atrial fibrillation to decrease the risk of stroke, but also for the treatment and prevention of venous thromboembolism [5]. Some genetic polymorphisms have been shown to be associated with the required dose and thereby also with the risk of adverse treatment outcomes, such as bleeding or thromboembolism [2]. Polymorphisms in the *VKORC1* gene, coding for the main target enzyme of the drugs, and the *CYP2C9* gene, coding for the main metabolizing enzyme, together account for approximately one third of the variability in dose requirements among different patients [3,6]. Several dosing algorithms have therefore been developed including genetic information, next to patient characteristics such as age, gender, height and weight [7].

Until recently, the clinical effectiveness of these algorithms have not been tested in acenocoumarol or phenprocoumon users. For warfarin users, some trials have been published, but these were not able to provide convincing evidence [7]. By the end of 2013, three large randomized controlled trials on pharmacogenetic-guided dosing of coumarin anticoagulants had been published [8-10]. One of these trials included acenocoumarol users from The Netherlands and Greece and phenprocoumon users from The Netherlands [8]. In this trial (the acenocoumarol and phenprocoumon arms of the European Pharmacogenetics of Anticoagulant Therapy (EU-PACT) trial - NCT01119261 and NCT01119274), a pharmacogenetic-guided algorithm based on age, gender, height, weight, amiodarone use and *VKORC1* and *CYP2C9* genotype, was compared to an algorithm with the same patient characteristics, except the genotype information. This was done because it was expected that using an algorithm based on patient characteristics only, would already perform better than the current standard care (all patients receive the same dose during the first days of therapy and this dose is adjusted after measuring the anticoagulant effect using an International Normalized Ratio (INR) test).

The pharmacogenetic algorithm did not significantly improve the primary outcome of time in therapeutic INR range in the first 12 weeks of therapy. However, it did improve the time in therapeutic

INR range in the first 4 weeks (52.8% versus 47.5%, p=0.02) [8]. Because performing a genetic test to assess the patients' genotype will require extra costs, it is important to investigate the cost-effectiveness of this test. The aim of this study is therefore to investigate the cost-effectiveness of a pharmacogenetic dosing algorithm versus a clinical dosing algorithm for coumarin anticoagulants in The Netherlands. In The Netherlands, only phenprocoumon and acenocoumarol are prescribed (not warfarin). This study will therefore focus on phenprocoumon as well as acenocoumarol.

**Materials and methods**

*Model structure*

A decision-analytic Markov model was used to analyze the cost-effectiveness of a pharmacogenetic algorithm compared to a clinical algorithm for phenprocoumon and acenocoumarol. The model was similar to the model in two previous studies [11,12] and developed using TreeAge software (TreeAge Pro 2012). The base-case analysis consisted of a hypothetical cohort of Dutch patients with atrial fibrillation, aged 70 years [8,13], initiating coumarin anticoagulant therapy. Using this model, we compared the incidence of adverse events, quality-adjusted life-years (QALYs), and direct medical costs of pharmacogenetic dosing versus clinical dosing over a lifetime horizon.

Figure 1 shows the decision tree with the two treatment options. Patients were stratified by the number of variant alleles in either the *VKORC1* or the *CYP2C9* gene. The decision-analytic Markov model consisted of five health states: No event, thromboembolic event (ischemic stroke or transient ischemic attack (TIA)), Hemorrhagic event (intracranial hemorrhage (ICH) or extra cranial hemorrhage (ECH)), sequelae and death. All patients entered the model in the 'no event' state and could move to one of the other states at monthly intervals. When an event occurred, patient would stay in that state for one month and then move to no event, sequelae or death. Patients with a permanent disability after stroke or ICH went to the 'sequelae' state. Patients who recovered from an event went back to the 'no event' state and could have a recurrent event. All input parameters, except the time spent in INR range and the costs of genotyping, were equal for both treatment strategies.

Thromboembolic events consisted mainly of ischemic strokes, but 28% were assumed to be transient ischemic attacks (TIA) [14,15]. Patients with a stroke had a 10% chance of dying and 47% chance of sequelae [11,16]. The majority of hemorrhagic events (80%) were assumed to be extracranial hemorrhages (ECH), 20% were intracranial hemorrhages (ICH) [16,17]. The chance that an ICH would result in sequelae was 50% and the chance that it would be fatal was 45% [16,17]. Patients were assumed to switch to aspirin after an ICH [18,19] and it was assumed that all patients would recover after a TIA or ECH. Age-specific mortality rates were taken into account for all patients. Input parameters of the model are shown in Table 1.

*Clinical input*

The primary outcome of the EU-PACT trial was the percentage time spent in therapeutic INR range [8]. The trial was not powered to detect differences in adverse events, because of the relatively low rates of these events. We had access to individual patient data and could therefore perform additional analyses on the Dutch data from this trial (sponsored by Utrecht University) to determine the percentage time in different INR ranges (<2.0; 2.0–3.0; 3.0–5.0 and >5.0) in the first three months of the treatment in the different genotype groups. The percentage time in different INR ranges was calculated using linear interpolation as described by Rosendaal *et al.* [20] with IBM SPSS Statistics software, version 20. We used data from the Dutch Federation of Thrombosis Services for the time in the different ranges after the first three months. Supplementary Figure S1a+b show the percentage time spent in the different ranges in the control arm (clinical dosing) for phenprocoumon and acenocoumarol respectively.

The meta-analysis by Oake *et al*. [21] provided data on the incidence of thromboembolic and haemorrhagic events at different levels of INR. The proportion of thromboembolic events that were stroke or TIA and the proportion of haemorrhagic events that were ICH or ECH were used as described above and shown in Table 1. The specific event rates were thus calculated by multiplying the risk of an event at a specific INR level (from the meta-analysis, see also Table 1) by the proportion of that specific event and by the percentage time spent at that specific INR level.

The effect of genotyping on the percentage time in different INR ranges for the different genotypes was also derived from the Dutch EU-PACT data (Figure 2). Because no significant effect was found after the first 4 weeks, we only applied this effect to the first month of therapy [8]. After the first month, the percentage time spent in the different INR ranges was assumed to be equal to that of the patients in the control arm (clinical dosing). [21]

The frequency of INR measurements has been estimated at 21 per year [16] . In the first few months, this number is expected to be higher. In the first 3 months of the EU-PACT trial, 8 measurements of INR were planned. Analyzing the data showed that more INR measurements were performed, on average 6 measurements in the first month and 3 per month in the second and third months. We assumed 1 extra measurement after an adverse event.

*Quality of life and costs*

The quality of life for patients with atrial fibrillation in our model was 0.81 [22], a value which has been used in previous studies [11,12,23] and is similar to the value measured in the trial using the EQ5D questionnaire. A decrement in quality of life of 0.013 was applied for phenprocoumon or acenocoumarol use and a decrement of 0.002 for aspirin use [24]. Decrements were also ascribed when patients experienced an adverse event. In the case of a non-disabling event, these decrements were assumed to last 1 month. For patients in the 'sequelae' state a permanent decrement was applied. Table 2 shows QALY values and decrements for the different health states as well as the different costs applied in this study.

We have described in a previous review the different costs associated with coumarin anticoagulant therapy for different European countries, including The Netherlands [25]. We used these costs in our model unless more recent information was available [26-29]. The costs of a point-of-care genotyping test, which was used in the EU-PACT trial, have been estimated to cost approximately €40 [30]. The occurrence of a clinical event was associated with event-related costs. For non-disabling events (TIA, ECH and non-disabling stroke or ICH) no further costs were applied. For disabling stroke or ICH, also the costs of sequelae were added. Costs were determined from a healthcare sector perspective for the

year 2012 in Euros (€). While the Dutch guidelines recommend using a societal perspective, we used a healthcare sector perspective ; the costs incurred by others like the patient therefore fell outside the scope of this study. Effects were discounted at an annual rate of 1.5% and costs at an annual rate of 4%, as recommended in the national guidelines [31].

*Base case and sensitivity analyses*

Base-case estimates of the costs and QALYs of both algorithms were determined. Several sensitivity analyses were also performed. First, one-way sensitivity analyses were conducted to examine the impact of model parameters and assumptions on the results. The parameters were varied over their 95% confidence intervals; another plausible range was used (for example +/-20%) if a confidence interval was not available. Second, we performed a probabilistic sensitivity analysis using 10,000 Monte Carlo simulations to evaluate the combined impact of multiple model parameters on the estimated cost-effectiveness of a dosing algorithm using genotyping. Dirichlet distributions were used to vary the probabilities of the genotypes or the different outcomes of stroke and ICH (more than 2 possible results). Beta distributions were used for all other probabilities and QALYs, and gamma distributions for the costs. A normal distribution was used to vary the frequency of INR measurements and the effect of genotyping on percentage time spent in the different INR ranges. The built-in function of the TreeAge software was used to calculate distribution parameters using mean values, standard errors and alpha and beta values.

The Dutch guidelines do not use an official willingness to pay threshold, but €20,000 was often used in previous reimbursement decisions [32]. We therefore studied the chance pharmacogenetic-guided dosing would be cost-effective at the arbitrary threshold of €20,000 per QALY gained, but also varied this threshold over a wider range and showed the results in a cost-effectiveness acceptability curve. The cost-effectiveness acceptability curve displays the chance that genotyping would be cost-effective at various cost-effectiveness thresholds. Because genotyping costs are expected to decrease when the test is performed more frequently, we also performed a threshold analysis to see at what genotyping costs the

pharmacogenetic algorithm would be cost-effective, given a cost-effectiveness threshold of €20,000 per QALY gained.


**Results**

*Base case*

Table 3 shows the first year incidence of the clinical events per 100 patient-years for phenprocoumon and acenocoumarol for all patients and also per genotype separately. Overall, genotyping decreased the risk of hemorrhagic events by 0.03% and the risk of thromboembolic events by 0.02%. However, wild-type patients (carrying no variant alleles) and carriers of 1 variant allele had an increased risk of hemorrhagic events and carriers of 2 or more variant alleles (and carriers of 1 variant allele using acenocoumarol) had an increased risk of thromboembolic events when they were dosed using the pharmacogenetic algorithm. The difference in quality of the treatment between the two groups was only assumed to exist in the first month; after the first month, the quality of treatment, and therefore also the incidence of clinical events, remained the same.

Table 3 also shows the results of the cost-effectiveness analyses. Overall, costs were increased by €33 (95% CI: €12-€57 for phenprocoumon and €10-€59 for acenocoumarol and QALYs by 0.0012 (0.4 day in full health, 95% CI: -0.002-0.004) for phenprocoumon and by 0.0014 (0.5 day in full health, 95% CI: -0.002-0.005) for acenocoumarol.  The costs per QALY gained were €28,349 for phenprocoumon and €24,427 for acenocoumarol. These results also varied between the different genotypes. QALYs were decreased for phenprocoumon users carrying 2 or more variant alleles and for acenocoumarol users carrying 1 variant allele. For these patients, clinical dosing was dominant (less costly, more effective) to pharmacogenetic dosing.

The life expectancy (without quality adjustment) was 0.0014 years longer in the pharmacogenetic group (12.0393 vs 12.0379) for phenprocoumon and 0.0016 years longer (12.0382 vs 12.0366) for acenocoumarol.

*Sensitivity analyses*

Because of the large confidence intervals regarding the effect of genotyping, it can be expected that these parameters cause the largest uncertainty in our cost-effectiveness results. The percentage time spent with an INR<2 has the largest influence on the cost-effectiveness results of phenprocoumon. When this effect was very small (or the % time in INR<2 even increased), the QALYs decreased, so that the clinical dosing algorithm would be dominant. For acenocoumarol the largest influence was seen for the effect on percentage time spent with an INR>5 for carriers of 2 or more variants. Tornado diagrams showing the influence of the parameters regarding the effect of genotyping are shown in the Supplementary Figures 2a&b.The tornado diagrams in Figure 3 show the 10 parameters with the largest influence on the incremental cost-effectiveness ratio (ICER) in the one-way sensitivity analysis, excluding the parameters regarding the effect of genotyping. For both drugs, the age at the start of treatment (varied from 50 to 90 years) had the largest influence on the ICER. For younger patients, the cost-effectiveness would be more favourable than for older patients. The tornado diagrams in figure 3 all show positive cost-effectiveness ratios, meaning that genotyping was more effective with higher costs. Reduction in the effectiveness of genotyping could also lead to a combination of increased costs and decreased QALYs (resulting in negative cost-effectiveness ratios) compared with the clinical algorithm (see supplementary figures 2a&b).

In the majority of the simulations of the probabilistic sensitivity analysis (76% for phenprocoumon and 78% for acenocoumarol) the pharmacogenetic algorithms was more costly and more effective (Figure 4). At a willingness to pay threshold of €20,000 per QALY, the pharmacogenetic dosing algorithm was not likely to be cost-effective compared with the clinical dosing algorithm (30% chance for phenprocoumon and 36% chance for acenocoumarol). Figure 5 shows the probability that pharmacogenetic dosing would be cost-effective option over a range of likely thresholds. To keep the ICER below €20,000 per QALY gained, the costs of genotyping would have to be no more than €30 for phenprocoumon and €33 for acenocoumarol (Table 4). At a cost of €40 euro per test, pharmacogenetic

dosing would be cost-effective for phenprocoumon users aged ≤58 years or acenocoumarol users aged ≤64.

## Discussion

In this study, a pharmacogenetic dosing algorithm of phenprocoumon and acenocoumarol was shown to increase health care costs as well as QALYs, when compared to a clinical dosing algorithm. The increase in health was very small, only 0.0012 to 0.0014 QALY, which is equal to less than half a day in full health. The chance that the cost-effectiveness ratio was higher than the willingness to pay threshold of €20,000 per QALY gained was high, although the cost per QALY would be below this threshold if genotyping costs were to decrease to approximately €30. These results were found for patients aged 70 (our base case). For older patients, the costs of the test would have to be even lower for genotyping to be cost-effective. The cost-effectiveness would be more favorable for younger patients than for older patients. Because of the very small increase in health, cost-savings due to improved health are small as well, and therefore not likely to compensate for the costs of the genetic test. The difference in QALYs between the two options was expected to be small, because genotyping only reduces the incidence of adverse events in the first month. This difference could impact the quality of life over the rest of the patient's lifetime if the adverse event were to lead to permanent disability. The impact of thromboembolic events on the long-term quality of life would be somewhat higher that the impact of bleedings, due to the higher proportion of disabling events amongst thromboembolic events (34% vs 10% of bleedings).

Several cost-effectiveness studies have been published on pharmacogenetic-based warfarin dosing, with varying results as described in a systematic review [33]. Two studies from this review that reported the costs per QALY gained (also called a cost-utility analysis) [34,35] and a more recent study [11] all showed costs well above the willingness to pay threshold of $50,000 per QALY gained in the USA. There was still, however, large uncertainty in the cost-effectiveness, as there were no reliable results from well powered clinical trials available. Patrick *et al.* suggested that genotyping for warfarin should decrease out-of-range INR values by at least 5% in order to be cost-effective [36]. To date, only

one cost-effectiveness study focused on phenprocoumon [12] and also one on acenocoumarol [27], both in The Netherlands. In these studies, data from warfarin trials was used, because no trials on phenprocoumon or acenocoumarol were available. Based on those studies, pharmacogenetic dosing appeared to have a high chance to be cost-effective, although there was too much uncertainty to recommend genotyping. The present study is the first cost-effectiveness study based on data from a large clinical trial on genotyping for phenprocoumon and acenocoumarol and therefore provides a more reliable estimate of the cost-effectiveness of genotyping in The Netherlands than the previous studies on these drugs. A limitation, however, was that results from only one trial were available and 95% confidence intervals were still large, causing uncertainty in the cost-effectiveness results.

We used Dutch sources for the input parameters of the model whenever this data was available. For some parameters however, no Dutch data was available and we used international data instead (e.g., quality of life). However, we do not expect this to have a major influence on our results, because we do not expect large differences in these parameters between The Netherlands and other countries. The data on costs of the drugs and clinical events, which can differ largely between countries, were all from Dutch sources. Another limitation is the fact that the trial from which we derived the effectiveness data for this study was not powered to detect differences in bleeding or thromboembolic events. We therefore used INR as a surrogate parameter. The association between INR and risk of adverse events is an additional uncertainty in our study. We have varied the risk of bleeding and thromboembolic events in the different INR ranges in our sensitivity analysis to account for this uncertainty.

The guidelines for discounting in The Netherlands (higher rate for costs than for effects [31]) are slightly different than in many other countries, such as the UK where costs and effects are discounted at the same rate. This did not have a large influence on the results, however, because even though some events can have long-term consequences, most of the difference between the two strategies is seen in the first month.

The phenprocoumon and acenocoumarol arm of the EU-PACT trial [8] showed different results compared with the warfarin arm of the EU-PACT trial [9] and the COAG trial [10]. In the warfarin arm of

the EU-PACT trial, pharmacogenetic dosing was compared to standard care (the same initial dose for every patient) instead of a clinical algorithm (initial dose calculated using an algorithm that included the same demographic and clinical information as the algorithm in the genetic arm, such as age and concomitant medication) [9]. The difference in percentage time spent in therapeutic range between pharmacogenetic dosing and standard warfarin dosing was larger than the difference seen for phenprocoumon and acenocoumarol. One of the explanations for this difference is the fact that we compared a pharmacogenetic dosing algorithm to a clinical dosing algorithm. If true, both the effectiveness and cost-effectiveness of a pharmacogenetic algorithm would be more favorable if we had compared it with standard care instead of with a clinical dosing algorithm. The COAG trial found no difference between the pharmacogenetic algorithm and the clinical algorithm for warfarin in the USA [10]. These conflicting results have led to some confusion about the usefulness of genotyping, especially when compared to a clinical algorithm, which can be implemented without increasing costs.

**Conclusions**

For patients using phenprocoumon or acenocoumarol, pharmacogenetic dosing slightly increases health, but is unlikely to be cost-effective. However, this strategy could be cost-effective if the costs of genotyping would be low (<€30).

**Future perspective**

This study showed that if genotyping costs were to be low (<€30), a pharmacogenetic dosing algorithm could be cost-effective compared to a clinical algorithm for phenprocoumon and acenocoumarol in The Netherlands. If many patients undergo the test, the costs per test could decrease to less than €30. While the frequency of coumarin anticoagulant users requiring this test might decrease due to the increasing use of the new oral anticoagulants, such as dabigatran, rivaroxaban and apixaban, the worldwide number of users should remain large enough to make it attractive for industry to develop cheaper tests.

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Although the differences in cost-effectiveness results between the genotype groups cannot be used to recommend genotyping in certain patient groups only (since this is only known after testing), the results could be used to determine for which patients the algorithm needs to be improved in order to increase cost-effectiveness. It may be surprising that the clinical algorithm dominated the genetic algorithm in subgroups with variants (2 variants for phenprocoumon or 1 variant for acenocoumarol). This implies that the genetic algorithm did not work well in these subgroups. This might be improved by recalibrating the genetic algorithm for variant carriers in the future.

Before implementing genotyping in clinical practice, not only the cost-effectiveness should be considered, but also the total budget impact. Approximately 50,000 patients with atrial fibrillation started using acenocoumarol or phenprocoumon in 2011. With an additional cost of €33 per patient, genotyping all these new users would lead to a total cost of approximately €1.65 million per year.

**Executive summary**

*Introduction*

- Pharmacogenetic-guided dosing did not improve the quality of acenocoumarol and phenprocoumon treatment in the first 3 months of therapy, but it did improve the quality in the first 4 weeks of the treatment.

- The aim of this study was to investigate the cost-effectiveness of a pharmacogenetic dosing algorithm versus a clinical dosing algorithm for phenprocoumon and acenocoumarol in The Netherlands.

*Materials & methods*

- A decision-analytic Markov model was used to analyse the cost-effectiveness of a pharmacogenetic algorithm compared to a clinical algorithm for phenprocoumon and acenocoumarol.

- Data from the EU-PACT trial on percentage time spent in different International Normalized Ratio (INR) ranges was used to estimate differences in incidence of hemorrhagic and thromboembolic events between the pharmacogenetic algorithm and the clinical algorithm.

*Results*

- A pharmacogenetic dosing algorithm of phenprocoumon and acenocoumarol was shown to increase both health care costs and QALYs, when compared to a clinical dosing algorithm, but the increase in health was very small.

- At a willingness to pay threshold of €20,000 per QALY, the pharmacogenetic dosing algorithm was not likely to be cost-effective compared with the clinical dosing algorithm.

*Discussion*

- The cost-effectiveness ratio of pharmacogenetic dosing was higher than the willingness to pay threshold, although the cost per QALY would be below this threshold if genotyping costs were to decrease to approximately €30.

**References**

1. Lindh JD, Holm L, Andersson ML, Rane A: Influence of CYP2C9 genotype on warfarin dose requirements--a systematic review and meta-analysis. *Eur. J. Clin. Pharmacol.* 65(4), 365-375 (2009).

2. Schalekamp T, de Boer A: Pharmacogenetics of oral anticoagulant therapy. *Curr Pharm Des* 16(2), 187-203 (2010).

3. Wadelius M, Chen LY, Lindh JD *et al.*: The largest prospective warfarin-treated cohort supports genetic forecasting. *Blood* 113(4), 784-92 (2009).

4. Yang L, Ge W, Yu F, Zhu H: Impact of VKORC1 gene polymorphism on interindividual and interethnic warfarin dosage requirement--a systematic review and meta analysis. *Thromb. Res.* 125(4), e159-66 (2010).

5. Hirsh J, Dalen J, Anderson DR *et al.*: Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic range. *Chest* 119(1 Suppl), 8S-21S (2001).

6. Bodin L, Verstuyft C, Tregouet DA *et al.*: Cytochrome P450 2C9 (CYP2C9) and vitamin K epoxide reductase (VKORC1) genotypes as determinants of acenocoumarol sensitivity. *Blood* 106(1), 135-40 (2005).

7. Verhoef TI, Redekop WK, Daly AK, van Schie RM, de Boer A, Maitland-van der Zee AH: Pharmacogenetic-guided dosing of coumarin anticoagulants: algorithms for warfarin, acenocoumarol and phenprocoumon. *Br. J. Clin. Pharmacol.* 77(4), 626-641 (2014).

8. Verhoef TI, Ragia G, de Boer A *et al.*: A randomized trial of genotype-guided dosing of acenocoumarol and phenprocoumon. *N. Engl. J. Med.* 369(24), 2304-2312 (2013).
** Large randomized trial investigating a pharmacogenetic algorithm compared to a clinical algorithm for acenocoumarol and phenprocoumon in The Netherlands and Greece.

9. Pirmohamed M, Burnside G, Eriksson N *et al.*: A randomized trial of genotype-guided dosing of warfarin. *N. Engl. J. Med.* 369(24), 2294-2303 (2013).

** Large randomized trial investigating a pharmacogenetic algorithm compared to standard care for warfarin in the UK and Sweden.

10. Kimmel SE, French B, Kasner SE *et al.*: A pharmacogenetic versus a clinical algorithm for warfarin dosing. *N. Engl. J. Med.* 369(24), 2283-2293 (2013).

** Large randomized trial investigating a pharmacogenetic algorithm compared to a clinical algorithm for warfarin in the United States.

11. Meckley LM, Gudgeon JM, Anderson JL, Williams MS, Veenstra DL: A policy model to evaluate the benefits, risks and costs of warfarin pharmacogenomic testing. *Pharmacoeconomics* 28(1), 61-74 (2010).

* A cost-effectiveness analysis of pharmacogenetic warfarin dosing, using the surrogate end point of percentage time spent in therapeutic INR range.

12. Verhoef TI, Redekop WK, Veenstra DL *et al.*: Cost-effectiveness of pharmacogenetic-guided dosing of phenprocoumon in atrial fibrillation. *Pharmacogenomics* 14(8), 869-883 (2013).

* A cost-effectiveness analysis of pharmacogenetic phenprocoumon dosing, using the surrogate end point of percentage time spent in therapeutic INR range.

13. van Schie RM, Wessels JA, le Cessie S *et al.*: Loading and maintenance dose algorithms for phenprocoumon and acenocoumarol using patient characteristics and pharmacogenetic data. *Eur. Heart J.* 32(15), 1909-1917 (2011).

14. Shah SV, Gage BF: Cost-effectiveness of dabigatran for stroke prophylaxis in atrial fibrillation. *Circulation* 123(22), 2562-2570 (2011).

15. O'Brien CL, Gage BF: Costs and effectiveness of ximelagatran for stroke prophylaxis in chronic atrial fibrillation. *JAMA* 293(6), 699-706 (2005).

16. Federation of Dutch Anticoagulant clinics; Samenvatting medische jaarverslagen 2012. Available from: http://www.fnt.nl/media/docs/jaarverslagen/FNT_Medisch_jaarverslag_2012_WEB.pdf.

17. Fang MC, Go AS, Chang Y *et al.*: Death and disability from warfarin-associated intracranial and extracranial hemorrhages. *Am. J. Med.* 120(8), 700-705 (2007).

18. Hart RG, Pearce LA, Aguilar MI: Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann. Intern. Med.* 146(12), 857-867 (2007).

19. Connolly SJ, Eikelboom J, Joyner C *et al.*: Apixaban in patients with atrial fibrillation. *N. Engl. J. Med.* 364(9), 806-817 (2011).

20. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briet E: A method to determine the optimal intensity of oral anticoagulant therapy. *Thromb. Haemost.* 69(3), 236-239 (1993).

21. Oake N, Jennings A, Forster AJ, Fergusson D, Doucette S, van Walraven C: Anticoagulation intensity and outcomes among patients prescribed oral anticoagulant therapy: a systematic review and meta-analysis. *CMAJ* 179(3), 235-244 (2008).

22. Sullivan PW, Lawrence WF, Ghushchyan V: A national catalog of preference-based scores for chronic conditions in the United States. *Med. Care* 43(7), 736-749 (2005).

23. Sullivan PW, Arant TW, Ellis SL, Ulrich H: The cost effectiveness of anticoagulation management services for patients with atrial fibrillation and at high risk of stroke in the US. *Pharmacoeconomics* 24(10), 1021-1033 (2006).

24. Gage BF, Cardinalli AB, Owens DK: The effect of stroke and stroke prophylaxis with aspirin or warfarin on quality of life. *Arch. Intern. Med.* 156(16), 1829-1836 (1996).

25. Verhoef TI, Redekop WK, van Schie RM *et al.*: Cost-effectiveness of pharmacogenetics in anticoagulation: international differences in healthcare systems and costs. *Pharmacogenomics* 13(12), 1405-1417 (2012).

26. Dutch drug costs. Available from: www.medicijnkosten.nl.

27. Schalekamp T, Boink GJ, Visser LE, Stricker BH, de Boer A, Klungel OH: CYP2C9 genotyping in acenocoumarol treatment: is it a cost-effective addition to international normalized ratio monitoring? *Clinical pharmacology and therapeutics* 79(6), 511-20 (2006).

28. Struijs JN, van Genugten ML, Evers SM, Ament AJ, Baan CA, van den Bos GA: Future costs of stroke in the Netherlands: the impact of stroke services. *Int. J. Technol. Assess. Health Care* 22(4), 518-524 (2006).

29. Roos YB, Dijkgraaf MG, Albrecht KW *et al.*: Direct costs of modern treatment of aneurysmal subarachnoid hemorrhage in the first year after diagnosis. *Stroke* 33(6), 1595-1599 (2002).

30. Howard R, Leathart JB, French DJ *et al.*: Genotyping for CYP2C9 and VKORC1 alleles by a novel point of care assay with HyBeacon(R) probes. *Clin. Chim. Acta* 412(23-24), 2063-2069 (2011).

* This article describes a new point-of-care method for genotyping *CYP2C9* and *VKORC1*.

31. Hakkaart-van Roijen L, Tan SS, Bouwmans CAM: Handleiding voor kostenonderzoek. Methoden en standaard kostprijzen voor economische evaluaties in de gezondheidszorg. *Instituut voor Medical Technology Assessment, Erasmus Universiteit Rotterdam, in opdracht van het College voor Zorgverzekeringen.* (2010).

32. Stolk EA, van Donselaar G, Brouwer WB, Busschbach JJ: Reconciliation of economic concerns and health policy: illustration of an equity adjustment procedure using proportional shortfall. *Pharmacoeconomics* 22(17), 1097-1107 (2004).

33. Verhoef TI, Redekop WK, Darba J *et al.*: A systematic review of cost-effectiveness analyses of pharmacogenetic-guided dosing in treatment with coumarin derivatives. *Pharmacogenomics* 11(7), 989-1002 (2010).

34. Eckman MH, Rosand J, Greenberg SM, Gage BF: Cost-effectiveness of using pharmacogenetic information in warfarin dosing for patients with nonvalvular atrial fibrillation. *Annals of internal medicine* 150(2), 73-83 (2009).

35. You JH, Tsui KK, Wong RS, Cheng G: Potential Clinical and Economic Outcomes of CYP2C9 and VKORC1 Genotype-Guided Dosing in Patients Starting Warfarin Therapy. *Clinical pharmacology and therapeutics* 86(5), 540-547 (2009).

36. Patrick AR, Avorn J, Choudhry NK: Cost-Effectiveness of Genotype-Guided Warfarin Dosing for Patients With Atrial Fibrillation. *Circ Cardiovasc Qual Outcomes* 2(5), 429-436 (2009).