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

Authors: Talitha I Verhoef, William K Redekop, Anthonius de Boer and Anke Hilse Maitland-van der Zee
Date: Jan. 2015
From: Pharmacogenomics(Vol. 16, Issue 2)
Publisher: Future Medicine Ltd.
Document Type: Article
Length: 6,628 words
DOI: http://dx.doi.org.proxy.library.uu.nl/10.2217/pgs.14.149

Full Text:
Author(s): Talitha I Verhoef [aff1] [aff2] , William K Redekop [aff3] , Anthonius de Boer [aff1] , Anke Hilse Maitland-van der Zee [*] [aff1]

Keywords:

acenocoumarol; atrial fibrillation; health economics; pharmacogenetics; phenprocoumon

Background

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 had 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 with an algorithm with the same patient characteristics, except the genotype information. This was done because it was expected that an algorithm based on patient characteristics only would 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 vs 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 & methods

Model structure

A decision-analytic Markov model was used to analyze the cost-effectiveness of a pharmacogenetic algorithm compared with 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 extracranial 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, the patient would stay in that state for 1 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 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 ECH, and 20% were 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 ([less than]2.0, 2.0-3.0, 3.0-5.0 and [greater than]5.0) in the first 3 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* . [21] 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 3 months. Supplementary Figures 1A & B (see online at: www.futuremedicine.com/doi/suppl/10.2217/pgs.14.149) 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* . [20] provided data on the incidence of thromboembolic and hemorrhagic events at different levels of INR. The proportion of thromboembolic events that were stroke or TIA and the proportion of hemorrhagic 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) [20].

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, eight measurements of INR were planned. Analyzing the data showed that more INR measurements were performed, on average six measurements in the first month and three per month in the second and third months. We assumed one extra measurement after an adverse event.

Quality of life & costs

The quality of life for patients with atrial fibrillation in our model was 0.81 [22], a value that 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 nondisabling 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 [26]. We used these costs in our model unless more recent information was available [25,27,28,30]. The costs of a point-of-care genotyping test, which was used in the EU-PACT trial, have been estimated to cost approximately E40 [31]. The occurrence of a clinical event was associated with event-related costs. For nondisabling events (TIA, ECH and nondisabling stroke or ICH), no further costs were applied. For disabling stroke or ICH, the costs of sequelae were added. Costs were determined from a healthcare sector perspective for the year 2012 in Euros (E). 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 [32].

Base case & 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 (e.g., ±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 two 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 E20,000 was often used in previous reimbursement decisions [33]. We therefore studied the chance that pharmacogenetic-guided dosing would be cost effective at the arbitrary threshold of E20,000 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 E20,000 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 one variant allele had an increased risk of hemorrhagic events and carriers of two or more variant alleles (and carriers of one 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 E33 (95% CI: E12-57 for phenprocoumon and E10-59 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 E28,349 for phenprocoumon and E24,427 for acenocoumarol. These results also varied between the different genotypes. QALYs were decreased for phenprocoumon users carrying two or more variant alleles and for acenocoumarol users carrying one 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 [less than]2 has the largest influence on the cost-effectiveness results of phenprocoumon. When this effect was very small (or the percentage time in INR [less than]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 [greater than]5 for carriers of two 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 ten 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 favorable than for older patients. The tornado diagrams in Figure 3 all show positive cost-effectiveness ratios, indicating 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 algorithm was more costly and more effective (Figure 4). At a willingness-to-pay threshold of E20,000 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 a cost-effective option over a range of likely thresholds. To keep the ICER below E20,000 per QALY gained, the costs of genotyping would have to be no more than E30 for phenprocoumon and E33 for acenocoumarol (Table 4). At a cost of E40 per test, pharmacogenetic dosing would be cost effective for phenprocoumon users aged [less than or equal to]58 years or acenocoumarol users aged [less than or equal to]64 years.

Discussion

In this study, a pharmacogenetic dosing algorithm of phenprocoumon and acenocoumarol was shown to increase healthcare costs as

well as QALYs when compared with a clinical dosing algorithm. The increase in health was very small, only 0.0012-0.0014 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 E20,000 per QALY gained was high, although the cost per QALY would be below this threshold if genotyping costs were to decrease to approximately E30. These results were found for patients aged 70 years (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 owing 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, owing 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 [34]. Two studies from this review that reported the costs per QALY gained (also called a cost-utility analysis) [35,36] 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 [37]. To date, only one cost-effectiveness study focused on phenprocoumon [12] and one on acenocoumarol [27], both in The Netherlands. In these studies, data from warfarin trials were used, because no trials on phenprocoumon or acenocoumarol were available. Based on those studies, pharmacogenetic dosing appeared to have a high chance of being 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 these data were available. For some parameters, however, no Dutch data were 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 [32]) 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 with 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 e.g., 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 with a clinical algorithm, which can be implemented without increasing costs.

Conclusion

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 were low ([less than]E30).

Future perspective

This study showed that if genotyping costs were low ([less than]E30), a pharmacogenetic dosing algorithm could be cost effective compared with 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 E30. While the frequency of coumarin anticoagulant users requiring this test might decrease owing 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.

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 (two variants for phenprocoumon or one 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 into clinical practice, the total budget impact should be considered as well as the cost-effectiveness. Approximately 50,000 patients with atrial fibrillation started using acenocoumarol or phenprocoumon in 2011. With an additional cost of E33 per patient, genotyping all these new users would lead to a total cost of approximately E1.65 million per year.

Table 1. Clinical input parameters for the model.

Parameter	Base case	Range	Distribution	Ref.
Genotype				
Wild-type	0.28	0.23-0.33	Dirichlet	[dagger]
1 variant allele	0.36	0.31-0.41	Dirichlet	[dagger]
[greater than or equal to]2 variant alleles	0.36	0.31-0.42	Dirichlet	[dagger]
Risk of bleeding (yearly)				
INR [less than]2	0.015	0.007-0.030	Beta	[20]
INR within range	0.014	0.009-0.023	Beta	[20]
INR 3.0-5.0	0.037	0.022-0.063	Beta	[20]
INR [greater than]5	0.301	0.149-0.609	Beta	[20]
Aspirin	0.012	0.008-0.019	Beta	[19]
Risk of TE (yearly)				
INR [less than]2	0.081	0.043-0.151	Beta	[20]
INR within range	0.024	0.012-0.049	Beta	[20]
INR 3.0-5.0	0.027	0.012-0.062	Beta	[20]
INR [greater than]5	0.073	0.039-0.136	Beta	[20]
Aspirin	0.030	0.020-0.044	Beta	[19]
Bleeding outcomes (if bleeding occurs)				
ICH	0.20	0.19-0.21	Beta	[16]
- Fatal	0.45	0.42-0.49	Dirichlet	[16]
- Sequelae	0.50	0.46-0.54	Dirichlet	[17]
ECH	0.80	0.79-0.81	Beta	[17]
TE outcomes (if TE occurs)				
Stroke	0.72	0.69-0.75	Beta	[14,15]
- Fatal	0.10	0.08-0.13	Dirichlet	[16]
- Sequelae	0.47	0.44-0.51	Dirichlet	[11]
Death/month in case of sequelae	0.056	0.04-0.07	Beta	[11]
TIA	0.28	0.25-0.31	Beta	[14,15]
INR measurements				
				[dagger]

First month	6	4.27-7.73	Normal	
Months 2 and 3, per month	3	1.15-4.85	Normal	[dagger]
Consecutive months, per month	1.75	1.23-2.14	Normal	[16]
Extra measurement after event	1	0-2	Uniform	Assumption
Age				
Age at start of treatment, years	70	50-90	Normal	[8,13]

[dagger] Authors' own analysis of data from the EU-PACT trial [8].

ECH: Extracranial hemorrhage; ICH: Intracranial hemorrhage; INR: International normalized ratio; TE: Thromboembolic event; TIA: Transient ischemic attack.

Table 2. Utilities and costs.

Parameter	Base case	Range	Distribution	Ref.
Utilities				
Atrial fibrillation	0.81	0.7784 to 0.8430	Beta	[22]
Coumarin use	-0.013	-0.005 to -0.021	Beta	[24]
Aspirin use	-0.002	0.000 to -0.006	Beta	[24]
ECH	-0.06	-0.02 to -0.10	Beta	[11]
ICH	-0.1814	-0.1550 to -0.2089	Beta	[22]
TIA	-0.1032	-0.0881 to -0.1189	Beta	[22]
Stroke	-0.1385	-0.1182 to -0.1600	Beta	[22]
Sequelae after ICH or stroke	-0.374	-0.160 to -0.588	Beta	[22]
Costs (E)				
Genotyping	40	20 to 60	Gamma	[25]
Phenprocoumon tablets per month	1.78	1.53 to 2.03	Gamma	[25]
Acenocoumarol tablets per month	1.49	1.24 to 1.74	Gamma	[25]
Aspirin tablets per month	0.90	0.79 to 1.01	Gamma	[25]
INR measurement + visit to anticoagulant clinic	12.07	10 to 14	Gamma	[12,26,27]
ECH	13,690	10,952 to 16,428	Gamma	[12,26,27]
ICH	19,672	15,737 to 23,606	Gamma	[12,26,28]
TIA	949	759 to 1139	Gamma	[29]
Stroke	10,282	8226 to 12,338	Gamma	[12,26,30]
Sequelae - first month	9254	7403 to 11,105	Gamma	[12,26]
Sequalae - subsequent months	463	370 to 555	Gamma	[12,26]

ECH: Extracranial hemorrhage; ICH: Intracranial hemorrhage; INR: International normalized ratio; TIA: Transient ischemic attack.

Table 3. Results of the cost-effectiveness analysis: base case.

Population	Strategy	First-year incidence of adverse events per 100 patients		Lifelong outcomes		
Hemorrhagic	Thromboembolic	Costs (E)		QALYs	ICER (E/QALY gained)	
Phenprocoumon						
Overall	Clinical	2		3.03	9644	9.5198
Pharmacogenetic	1.97	3.01		9677	9.5210	
Δ	-0.03	-0.02		33	0.0012	28,349
Wild-type	Clinical	1.92		3.18	9647	9.5160
Pharmacogenetic	1.94	3.08		9679	9.5192	
Δ	0.02	-0.10		32	0.0033	9788
1 variant	Clinical	1.90		3.06	9633	9.5205
Pharmacogenetic	1.93	3.01		9671	9.5219	
Δ	0.03	-0.05		38	0.0014	27,820
2 variants	Clinical	2.17		2.9	9652	9.5221
Pharmacogenetic	2.06	2.97		9682	9.5215	
Δ	-0.11	0.07		29	-0.0007	Clinical dosing dominates
Acenocoumarol						
Overall	Standard	2.05		3.05	9616	9.5187
Pharmacogenetic	2.02	3.03		9649	9.5201	
Δ	-0.03	-0.02		33	0.0014	24,427
Wild-type	Standard	1.86		3.2	9605	9.5164
Pharmacogenetic	1.91	3.08		9638	9.5201	
Δ	0.05	-0.12		34	0.0037	9069
1 variant	Standard	1.97		3.02	9604	9.5211
Pharmacogenetic	2.01	3.03		9652	9.5197	
Δ	0.04	0.01		48	-0.0014	Clinical dosing dominates
2 variants	Standard	2.26		2.96	9637	9.5182
Pharmacogenetic	2.10	2.98		9656	9.5204	
Δ	-0.16	0.02		18	0.0022	8101

ICER: Incremental cost-effectiveness ratio; QALY: Quality-adjusted life-year.

Table 4. Threshold values for age and costs of genotyping at which the incremental cost-effectiveness ratio would be below E20,000 per quality-adjusted life-year gained.

	ICER [less than or equal to]E20,000	ICER [greater than]E20,000
Phenprocoumon		

Age	[less than or equal to]58 years	[greater than]58 years
Cost of the test	[less than or equal to]E30	[greater than]E30
Acenocoumarol		
Age	[less than or equal to]64 years	[greater than]64 years
Cost of the test	[less than or equal to]E33	[greater than]E33

ICER: Incremental cost-effectiveness ratio.

Executive summary

Background

* 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 analyze the cost-effectiveness of a pharmacogenetic algorithm compared with a clinical algorithm for phenprocoumon and acenocoumarol.

* Data from the EU-PACT trial on percentage time spent in different international normalized ratio ranges were 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 healthcare costs and quality-adjusted life-years (QALYs), when compared with a clinical dosing algorithm, but the increase in health was very small.

* At a willingness-to-pay threshold of E20,000 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 E30.

CAPTION(S):

Figure 1. Decision tree and Markov model.

(A) The decision tree shows that patients initiating coumarin anticoagulant therapy could be treated by one of the two dosing algorithms with different chances of developing adverse events in each genotype group. For each genotype group a **(B)** Markov model (M) was applied, which included the following health states: no event, thromboembolic event (stroke or transient ischemic attack), hemorrhagic event (intracranial or extracranial hemorrhage), sequelae and death. After a thromboembolic or hemorrhagic event patients move to either no event (i.e., no sequelae), sequelae or death.

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Papers of special note have been highlighted as: * of interest; ** of considerable interest

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Author Affiliation(s):

[1] Utrecht Institute of Pharmaceutical Sciences, Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht University, Utrecht, The Netherlands

[2] Department of Applied Health Research, University College London, London, UK

[3] Institute for Medical Technology Assessment, Erasmus University, Rotterdam, The Netherlands

Author Note(s):

*Author for correspondence: a.h.maitland@uu.nl

[double dagger] Rita Barallon, LGC Limited, Middlesex, UK; Anthonius de Boer, Utrecht University, Utrecht, The Netherlands; Ann Daly, Newcastle University, Newcastle upon Tyne, UK; Elisabeth Haschke-Becher, Elisabethinen Hospital Linz, Linz, Austria; Farhad Kamali, Newcastle University, Newcastle upon Tyne, UK; Anke-Hilse Maitland-van der Zee, Utrecht University, Utrecht, The Netherlands; Ken Redekop, Erasmus University, Rotterdam, The Netherlands; Julia Stingl, Humboldt University of Berlin, Berlin, Germany; Vangelis G Manolopoulos, Democritus University of Thrace, Alexandroupolis, Greece; Munir Pirmohamed, University of Liverpool, Liverpool, UK; Frits R Rosendaal, Leiden University Medical Center, Leiden, The Netherlands; Mia Wadelius, Uppsala University, Uppsala, Sweden

Financial & competing interests disclosure

This work was supported by the European Community's Seventh Framework Programme under grant agreement HEALTH-

F2-2009-223062. AH Maitland-van der Zee reports an unrestricted grant from GSK, outside the submitted work. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Talitha I Verhoef, William K Redekop, Anthonius de Boer, Anke Hilse Maitland-van der Zee