For reprint orders, please contact reprints@expert-reviews.com

EXPERT REVIEWS

Clinical and economic consequences of pharmacogenetic-guided dosing of warfarin

Expert Rev. Pharmacoeconomics Outcomes Res. 10(4), 375–378 (2010)

Talitha I Verhoef[1], Tom Schalekamp[1], William K Redekop[2], Anthonius de Boer[1] and Anke-Hilse Maitland-van der Zee[†1]

[1]Utrecht University, Faculty of Science, Division of Pharmacoepidemiology and Pharmacotherapy, PO Box 80 082, 3508 TB Utrecht, The Netherlands
[2]Institute for Medical Technology Assessment, Erasmus University, Rotterdam, The Netherlands
[†]Author for correspondence:
Tel.: +31 302 534 042
Fax: +31 302 539 166
a.h.maitland@uu.nl

Evaluation of: 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).

Patients using warfarin for oral anticoagulant therapy need to be frequently monitored because of warfarin's narrow therapeutic range and the large variation in dose requirements among patients. Patients receiving the wrong dose have an increased risk of bleeding or thromboembolic events. The required dose is influenced by environmental factors, such as gender, age, diet and concomitant medication, as well as genetic factors. Pharmacogenetic testing prior to warfarin initiation might improve dosing accuracy and, therefore, safety and efficacy of warfarin treatment. Meckley *et al*. studied the clinical consequences and costs of genotyping before warfarin treatment. The results of their study suggest that pharmacogenetic-guided dosing of patients initiating warfarin could improve health (quality-adjusted life-years) but at a high cost per quality-adjusted life-year gained. Owing to the inevitable assumptions that have to be made in all cost–effectiveness models, great uncertainty remains regarding the cost–effectiveness of pharmacogenetic-guided warfarin dosing.

Keywords: *CYP2C9* • economics • pharmacogenetics • *VKORC1* • warfarin

Warfarin is a drug widely used for oral anticoagulation in patients with atrial fibrillation, venous thromboembolism or a prosthetic heart valve to reduce the risk of thromboembolic events [1]. The optimal warfarin dose is assessed by measuring the international normalized ratio (INR), which should be kept within a narrow range, since the risk of thromboembolic events decreases with an increasing INR, while the risk of bleeding events increases. A large inter- and intra-patient variability in warfarin dose requirement makes frequent INR monitoring necessary. The required dosage is influenced by several factors, such as gender, age, diet, concomitant medication and genetic factors.

Polymorphisms in both the *CYP2C9* gene, encoding for the main metabolizing enzyme, cytochrome P450 2C9 (CYP2C9), and the *VKORC1* gene, encoding the target enzyme vitamin K epoxide reductase multiprotein complex 1, explain approximately a third of the variation in warfarin dose requirement. Information regarding the genotype of a patient can therefore be used to predict the warfarin maintenance dose. Although the ability of genotype-guided dosing to improve the safety and efficacy of warfarin treatment has been investigated in a few small randomized controlled trials, there is still no clear evidence about the effectiveness of this dosing strategy [2].

The economic impact of genotyping patients prior to warfarin use is also not clear. Results from cost–effectiveness analyses of warfarin pharmacogenetics (using genetic information to determine the required dose) do not all point in the same direction [3–5]. In one of these studies genotyping appeared to be the dominant strategy, meaning that genotyping was more effective and less costly than not genotyping [4]. By contrast, other studies found that the gain in effectiveness was coupled with higher costs [3,5]. In most studies the effect of genotyping was based directly on its observed or assumed impact on the risk of bleeding and thromboembolic

 10.1586/ERP.10.42 © 2010 Expert Reviews Ltd ISSN 1473-7167

events, although the studies performed to date have not been large enough to detect reductions of adverse events. Using the association between the level of INR with the risk of bleeding and thromboembolic events, Meckley *et al.* developed a policy model to evaluate the clinical and economic consequences of pharmacogenetic-guided warfarin dosing, based on the effect of genotyping on INR levels [1].

Summary of methods & results

In their study Meckley *et al.* developed a decision analytic Markov model to perform an economic evaluation comparing genotype-guided dosing with standard anticoagulation care using a lifetime horizon [1]. The base-case scenario focused on 65-year-old patients with atrial fibrillation who were initiated on long-term treatment with warfarin. Patients were stratified by genotype into three different groups: the first group consisted of *CYP2C9* wild-type/*VKORC1* wild-type patients, the second of *CYP2C9* wild-type/*VKORC1* variant patients, and in the last group were the *CYP2C9* variants. This last group was not stratified by *VKORC1* genotype for group size reasons. All patients entered the Markov model in a healthy ('well') state and could move from this state to the states 'clot', 'bleed', 'sequelae' or 'death' in monthly cycles. The probabilities to experience a major bleeding or thromboembolic event were based on the time spent within, above or below therapeutic INR range. The time patients spent within, above and below therapeutic INR range was based on data from the COUMAGEN trial [6]. This trial provided data on the difference in time spent in therapeutic INR range between the genotype-guided dosing group and the standard dosing group, but the authors reanalyzed the COUMAGEN data in order to obtain additional information regarding the time spent above or below this range. The differences in time spent within the different INR ranges between the two dosing strategies were used in the model for the first month and reduced to zero in the sixth month of therapy. An increased bleeding risk of 2.26, independent of the effect of INR, was assumed from a meta-analysis for the *CYP2C9* variant patients, which was subjected to sensitivity analysis [7].

Utility (or quality-of-life) scores for the different health states were used to calculate the difference in quality-adjusted life-years (QALYs) between the standard and the genotype-guided dosing group. Genotyping itself was assumed to have no effect on the quality of life of the patient. The difference in costs between the two strategies was calculated and included only direct medical costs, since the authors applied a third party payer perspective. One-way sensitivity analyses were performed for all input parameters over prespecified ranges and several scenario analyses were conducted. The chance that the incremental cost–effectiveness ratio (ICER) would fall below a certain willingness-to-pay threshold (e.g., US$50,000 per QALY gained) was calculated in a probabilistic sensitivity analysis using Monte Carlo simulations.

Meckley *et al.* found that pharmacogenetics could reduce the time spent above therapeutic INR range in the *CYP2C9* variant group by 15%, and the time spent below therapeutic range in the *CYP2C9* wild-type/*VKORC1* wild-type group by 8% [1]. In the third group (*CYP2C9* wild-type/*VKORC1* variants) there were no differences in time spent above or below therapeutic INR range between the two dosing strategies. In the base case analysis the incidence of bleedings was reduced by 0.17%, the incidence of thromboembolic events increased by 0.03% and incidence of death reduced by 0.13% in the pharmacogenetic-guided dosing group. These differences resulted in a QALY increase of 0.0027. As genotyping also led to an overall cost increase of US$162, the ICER was US$60,725 per QALY gained. When looking at the ICERs in the different genotype groups, pharmacogenetic-guided dosing was most cost effective in the group consisting of *VKORC1* and *CYP2C9* wild-type patients. In this group there was a decrease in the risk of bleedings, thromboembolic events and deaths. The ICER for this group was US$13,500 per QALY gained. For the patients with *CYP2C9* variant alleles genotype-guided dosing was dominated by the standard dosing strategy, meaning that genotyping resulted in a decrease in QALYs and an increase in costs. This result arose because of an increase in the frequency of thromboembolic events in this group.

The uncertainty around the cost of a pharmacogenetic test, as investigated in the one-way sensitivity analysis, caused the largest part of the uncertainty around the cost–effectiveness ratio. In one of the scenario analyses, data from Caraco *et al.* were used instead of data from the COUMAGEN trial [8]. In this scenario, the genotyping strategy was the dominant strategy. Genotyping was also the dominant strategy when it was assumed that genotyping reduced the bleeding risk in *CYP2C9* variant patients further. The probabilistic sensitivity analysis revealed that there was a 15% chance that the pharmacogenetic-guided dosing was the dominant strategy. In addition, it was estimated that there was a 46% chance that the true ICER was below US$50,000 per QALY gained and a 67% chance that it was below US$100,000 per QALY gained.

Discussion

This study suggested that pharmacogenetic-guided dosing of warfarin could improve the health of patients initiating warfarin while also increasing healthcare costs compared with a standard dosing regimen. The probability that genotyping would cost less than US$50,000 per QALY gained was estimated to be almost 50%. However, owing to uncertainty regarding the values of several input parameters, Meckley *et al.* found that the possible impact of genotyping ranged from a possibility that genotype-guided dosing is the dominant strategy to a possibility that it is less effective and more costly than a standard dosing regimen [1]. This wide range of possible realities is mainly due to uncertainty regarding the effectiveness of pharmacogenetic-guided dosing on the risk of serious adverse events or therapeutic failure of warfarin therapy.

Patients with a variant genotype have a higher risk of bleedings due to warfarin therapy, because of a lower dose requirement. A genotype-guided dosing strategy might reduce this risk when patients with a variant genotype receive a lower dose. It is, therefore, remarkable that genotyping appeared to be less cost effective in patients with a variant genotype. This was explained by the increase in the number of thromboembolic events in this group, which might indicate that the dosages for these patients were overadjusted.

Since the clinical trials performed to date provide no direct evidence regarding the influence of genotyping on the incidence of adverse events or therapeutic failure, these authors used the time within, above and below therapeutic INR range as a surrogate for these clinical end points. This method has been used in two other studies investigating the cost–effectiveness of pharmacogenetic-guided dosing of warfarin [5,9]. In the study of Patrick *et al.,* data from the COUMAGEN trial [6] together with data from Caraco *et al.* [8] were used to calculate the effect of genotyping on the time spent within therapeutic INR range [9]. In a probabilistic sensitivity analysis Patrick *et al.* found a chance of 42% that genotyping would be cost effective given a willingness to pay of $50,000 per QALY [9], which is quite similar to the 46% in the study of Meckley *et al.* [1]. In the study of You *et al.* this chance was 38% [5] and the base case results were also less optimistic than in the Meckley *et al.* study [1], since they reported an ICER of $347,059 per QALY gained. In the study by You *et al.* lower baseline adverse event rates were used and the effect of genotyping was not stratified by genotype as in the current study. In the probabilistic sensitivity analysis by Meckley *et al.* the costs of the genetic test are also varied [1]. It would have been more useful to vary this parameter in a scenario analysis, because at the moment of decision-making the prices will be known already.

The development of this model using INR as a surrogate end point for bleedings and thromboembolic events seems very useful, as there is not enough evidence about the effect of genotyping on the adverse event rate. However, the uncertainty around the results of this study are still too large to allow any recommendations regarding the implementation of pharmacogenetics in treatment with warfarin. This uncertainty is mainly caused by the fact that there is not sufficient evidence regarding the effect of genotyping on INR ranges either, because this has only been investigated in a few small clinical trials. For some input parameters, such as the effect of genotyping on INR after the first month of therapy, the authors needed to make assumptions, because there is no evidence yet available on these parameters. Therefore, it is necessary to delay any recommendations regarding genotyping until more data from large clinical trials become available.

Expert commentary & five-year view

Pharmacogenetic-guided dosing of warfarin and other coumarin derivatives seems to be a promising new method to improve the safety and efficacy of oral anticoagulant therapy. Currently, the response to warfarin treatment is evaluated by INR measurement after the first few days of therapy. The prescribed dose can then be adapted to the patient's needs, so the patient will receive a more individualized dose after this first INR measurement. However, in the first few days of therapy, no information on the patient's response is available, so all patients receive the same loading dose. If patients were to be genotyped before they started taking warfarin, the loading dose for the first few days could already be personalized. However, this would only be possible if the genotype results are available before warfarin initiation. Therefore, it is desirable to have a fast, reproducible and accurate method to genotype; for this purpose, point-of-care testing might be useful.

Meckley *et al.* have shown that pharmacogenetic-guided dosing could improve health at higher healthcare costs compared with standard care, but there is not enough information available yet on the effectiveness of this genotype-guided dosing method [1]. Moreover, as the study of You *et al.* [5] demonstrates, a low adverse event rate with warfarin therapy will make genotyping less cost effective. As a consequence, the cost–effectiveness of pharmacogenetic-guided warfarin dosing will differ between countries and will be particularly favorable in settings where warfarin therapy is complicated by a relatively high rate of bleedings and thromboembolic events. The upcoming use of direct thrombin inhibitors might also reduce the value of genotype-guided warfarin dosing in the future to some extent.

It is not yet fully known how to use the genetic information to adjust the prescribed warfarin dose. In the study of Meckley *et al.* it seemed that patients with a variant genotype were underdosed in the pharmacogenetic-guided dosing strategy [1]. Dosing algorithms, such as the dosing algorithm developed by the International Warfain Pharmacogenetics Consortium [10], therefore need to be developed and tested widely to find the optimal way of adjusting the dose of warfarin or other coumarin derivatives according to the genetic information. It is also not yet clear whether the genetic information has any value for determining the right dose after the first few days of therapy, when the dose is also adjusted according to the INR values of the patients.

Within a few years, more data on this subject will become available, as several large clinical trials investigating the effectiveness of pharmacogenetic-guided dosing algorithms in treatment with warfarin and other coumarin derivatives are now underway [11,101]. Since the primary outcome of these studies is time within therapeutic INR range, a model like the one presented in this study of Meckley *et al.* [1] would be very useful to assess not only the effectiveness but also the cost–effectiveness of a pharmacogenetic-guided dosing strategy.

Key issues

- Polymorphisms in the *CYP2C9* and *VKORC1* genes can explain a large part of the variation in dose requirement of warfarin.
- Pharmacogenetic-guided dosing might improve the safety and efficacy of warfarin treatment, because sub- or supra-therapeutic dosages put patients at increased risk of thromboembolic events or bleedings.
- Genotype-guided dosing has been shown to improve health, but also increase healthcare costs.
- A large uncertainty remains around the effectiveness of genotyping patients prior to warfarin treatment, as well as around the economic consequences of this strategy.
- Data from large clinical trials are necessary to reduce this uncertainty.

Financial & competing interests disclosure

This project is funded by the European Community's Seventh Framework Programme under grant agreement HEALTH-F2-2009-223062. 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.

References

Papers of special note have been highlighted as:
•• of considerable interest

1 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).

2 Kurnik D, Loebstein R, Halkin H, Gak E, Almog S. 10 years of oral anticoagulant pharmacogenomics. What difference will it make? A critical appraisal. *Pharmacogenomics* 10(12), 1955–1965 (2009).

3 Eckman MH, Rosand J, Greenberg SM, Gage BF. Cost-effectiveness of using pharmacogenetic information in warfarin dosing for patients with nonvalvular atrial fibrillation. *Ann. Intern. Med.* 150(2), 73–83 (2009).

4 McWilliam A, Lutter R, Nardinelli C. Health care savings from personalizing medicine using genetic testing. the case of warfarin. *AEI-Brooking Joint Center for Regulatory Studies Working Paper 06–23*, (2006).

5 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. *Clin. Pharmacol. Ther.* 86(5), 540–547 (2009).

6 Anderson JL, Horne BD, Stevens SM *et al.* Randomized trial of genotype-guided versus standard warfarin dosing in patients initiating oral anticoagulation. *Circulation* 116(22), 2563–2570 (2007).

•• **Describes the first randomized trial investigating pharmacogenetic-guided dosing of warfarin based on both *CYP2C9* and *VKORC1*.**

7 Sanderson S, Emery J, Higgins J. *CYP2C9* gene variants, drug dose, and bleeding risk in warfarin-treated patients. A huge net systematic review and meta-analysis. *Genet. Med.* 7(2), 97–104 (2005).

8 Caraco Y, Blotnick S, Muszkat M. *CYP2C9* genotype-guided warfarin prescribing enhances the efficacy and safety of anticoagulation. A prospective randomized controlled study. *Clin. Pharmacol. Ther.* 83(3), 460–470 (2008).

9 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).

10 Klein TE, Altman RB, Eriksson N *et al.* Estimation of the warfarin dose with clinical and pharmacogenetic data. *N. Engl. J. Med.* 360(8), 753–764 (2009).

11 Van Schie RMF, Wadelius MI, Kamali F *et al.* Genotype-guided dosing of coumarin derivatives. The European Pharmacogenetics of Anticoagulant Therapy (EU-PACT) trial design. *Pharmacogenomics* 10(10), 1687–1695 (2009).

Website

101 Clarification of optimal anticoagulation through genetics research network http://coagstudy.org