PERSONALISED TREATMENT WITH ORAL ANTICOAGULANT DRUGS CLINICAL AND ECONOMIC ISSUES

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**Gepersonaliseerde behandeling met orale antistollingsmiddelen
Klinische en economische overwegingen
(met een samenvatting in het Nederlands)**

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GENERAL INTRODUCTION

Personalised medicine is a way to optimise treatment strategies by tailoring the treatment to the characteristics of an individual patient. These patient characteristics can include sex, age, height and weight, concomitant medication use or concomitant disease and biomarkers such as specific proteins in the blood. Also, information about a patient's DNA can be used to predict drug response. Pharmacogenetics/ genomics is a research field that studies variations in DNA sequence and the relation with drug response [1]. For the treatment of cardiovascular diseases several interactions between the DNA and drug response have been identified [2]. This information can be used to predict the chance that patients have less efficacy or more adverse drug reactions and adjust the dose or prescribe a different drug accordingly. Pharmacogenetics of treatment for cardiovascular disease is not implemented in clinical practice on a large scale yet. Although the FDA recommends the use of pharmacogenetic tests in the warfarin label, many are still waiting for more evidence on the effectiveness and cost-effectiveness [3].

Pharmacogenetics is already used in clinical practice for several drugs. For example, genotyping patients for HLA B*5701 is shown to be a cost-effective method to decrease the risk of a hypersensitivity reaction to abacavir, a human immunodeficiency virus-1 (HIV-1) nucleoside-analogue reverse transcriptase inhibitor [4]. Personalised medicine also appears to be useful in the treatment with coumarin anticoagulants. These oral anticoagulants have a narrow therapeutic range and a large variability in dose requirement among patients. A subtherapeutic dose may lead to therapy failure and thereby to an increased risk of stroke or systemic embolism, while a supratherapeutic dose leads to an increased risk of bleeding. Pharmacogenetic information can be used to predict the optimal dose before treatment initiation. During the late 1990s, an association between variations in the *CYP2C9* gene, coding for the main metabolising enzyme of coumarin anticoagulants, CYP2C9, and the required dose of warfarin was shown [5,6]. Later, genetic variations in other genes were also found to be associated with coumarin anticoagulant dose requirement. Variations in the *CYP2C9* gene and in the *VKORC1* gene (coding for the target enzyme of coumarin anticoagulants, VKORC1) together explain approximately one third of the dose variation [7,8]. Genotyping patients before the start with coumarin anticoagulants is expected to help the physicians prescribe the right dose and thereby increase the efficacy and safety of the treatment. Whether this is also clinically relevant will be investigated in a large European clinical trial, the European Pharmacogenetics of Anticoagulant Therapy (EU-PACT) trial [9]. In this trial the clinical utility of a pharmacogenetic-guided dosing algorithm will be investigated for acenocoumarol, phenprocoumon and warfarin in six European countries. The results from the EU-PACT trial will also be used to assess the cost-effectiveness of pre-treatment genotyping. It is important to study these economic issues because this information is required for implementation. For example,

health insurance companies often require information about the cost-effectiveness before reimbursement. The studies in this thesis were performed in preparation for the final EU-PACT analyses. The information provided in this thesis will be used as input for the cost-effectiveness analysis of the EU-PACT data.

OBJECTIVES OF THIS THESIS

The subject of this thesis is personalised treatment with oral anticoagulant drugs. A first objective of this thesis is to study genetic and other determinants that explain the variability in response to coumarin anticoagulants. A second objective is to study the economic consequences of different options (personalised medicine or using new oral anticoagulant drugs) to improve anticoagulant therapy.

OUTLINE OF THIS THESIS

This thesis starts with a background paper (chapter 2) on the use and characteristics of different coumarin anticoagulants, current clinical challenges and the role of pharmacogenetics in the treatment with these drugs. Part I of this thesis focuses on different determinants of variation in response to coumarin anticoagulants. In Chapter 3, we investigate the effects of *CYP2C9* and *VKORC1* genotype on anticoagulation control over time after initiating acenocoumarol treatment. Chapter 4 describes a similar study on the effects of *CYP2C9* and *VKORC1* genotype on phenprocoumon anticoagulation control in different time periods. In Chapter 5, we study the effect of omeprazole and esomeprazole on the maintenance dose of phenprocoumon and include the effect of the use of these drugs on the required maintenance dosage in a genotype-guided and a non-genotype-guided dosing algorithm. In Chapter 6, the beliefs coumarin anticoagulant users have about their therapy with acenocoumarol or phenprocoumon are described. These beliefs include the concerns patients might have about the drugs (for example about the side effects) and also beliefs about whether it is necessary for their health to use the drugs. We also compare the beliefs about coumarin anticoagulants with the beliefs about other cardiovascular drugs in users of an antihypertensive drug or statin. Insight into the beliefs about medicines can help to identify patients with a high risk of non-adherence to the therapy.

Part II of this thesis focuses on the cost-effectiveness of pharmacogenetic-guided dosing of coumarin anticoagulants, as well as the cost-effectiveness of new oral anticoagulants. Chapter 7 provides a review of cost-effectiveness studies on pharmacogenetic-guided coumarin dosing published up to the end of 2009. In Chapter 8, we evaluate a cost-effectiveness study on this subject, published in 2010, using the International Normalized Ratio (INR) as a surrogate endpoint to model the risk of adverse events. In Chapter 9, we use the model described in chapter 8 and adapt it to analyse the cost-effectiveness of
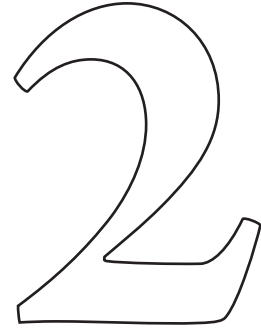
pharmacogenetic-guided phenprocoumon dosing in The Netherlands. Chapter 10 describes a review of current standards of coumarin anticoagulant therapy for atrial fibrillation and its associated costs in six different European countries. In Chapter 11, we conduct a cost-effectiveness analysis comparing three new oral anticoagulants for stroke prevention in patients with atrial fibrillation with coumarin anticoagulants in in a country with specialized anticoagulation clinics (The Netherlands) and in a country where the treatment of many patients with coumarin anticoagulants occurs in a primary care setting rather than a specialised anticoagulation clinic (the United Kingdom). Lastly, we discuss our findings in Chapter 12, putting the results in a broader perspective and describe the implications for (future) clinical practice and decision making.

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PHARMACOGENETIC-GUIDED DOSING
OF COUMARIN ANTICOAGULANTS:
ALGORITHMS FOR WARFARIN,
ACENOCOUMAROL AND PHENPROCOUMON

**Talitha I. Verhoef, William K. Redekop, Ann K. Daly, Rianne M. F. van Schie,
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ABSTRACT

Coumarin derivatives, such as warfarin, acenocoumarol and phenprocoumon are frequently prescribed oral anticoagulants to treat and prevent thromboembolism. Because there is a large inter-individual and intra-individual variability in dose-response and a small therapeutic window, treatment with coumarin derivatives is challenging. Certain polymorphisms in *CYP2C9* and *VKORC1* are associated with lower dose requirements and a higher risk of bleeding. In this review we describe the use of different coumarin derivatives, pharmacokinetic characteristics of these drugs and differences amongst the coumarin anticoagulants. We also describe the current clinical challenges and the role of pharmacogenetic factors. These genetic factors are used to develop dosing algorithms, and can be used to predict the right coumarin dose. The effectiveness of this new dosing strategy is currently being investigated in clinical trials.

INTRODUCTION

Coumarin derivatives are oral anticoagulants that are prescribed frequently to treat and prevent thromboembolism [1]. This group of drugs was discovered when several cows suffered fatal bleeding after eating stacks of spoiled sweet clover hay in the 1920s [2]. After several years, researchers were able to isolate and synthesise the first coumarin dicumarol. A more potent form of this drug, warfarin, initially used as rat poison, was introduced as oral anticoagulant in the 1950s and is currently the most widely used oral anticoagulant. Because warfarin and other coumarin derivatives inhibit the vitamin K-dependent synthesis of

biologically active clotting factors, they are also called Vitamin K antagonists.

In this review we will describe the use of different coumarin derivatives, pharmacokinetic characteristics of these drugs and differences amongst the coumarin anticoagulants. We will also describe the current clinical challenges and the role of pharmacogenetic factors. These genetic factors are included in dosing algorithms, which can be used to predict the right coumarin dose for an individual patient. The effectiveness of these new dosing algorithms is currently being investigated in clinical trials.

COUMARIN ANTICOAGULANTS; INDICATIONS

Coumarin anticoagulants are prescribed for different indications such as treatment and prevention of deep vein thrombosis or pulmonary embolism or prevention of systemic embolism or stroke in patients with prosthetic heart valves or atrial fibrillation [1]. Atrial fibrillation is the most frequent indication and has an estimated

prevalence in developed countries of 1.5 to 2% [3]. Patients with this cardiac arrhythmia have an increased risk of stroke and systemic embolism and warfarin use can reduce this risk by approximately 60% [4]. Anticoagulant therapy is therefore recommended in all patients with atrial fibrillation, except for patients with a very

low stroke risk (CHA$_2$DS$_2$-VASc score<1, i.e., patients with no other risk factors such as congestive heart failure, hypertension, age>65, diabetes mellitus, previous stroke or vascular disease) [3].

Patients with a prosthetic heart valve have an increased risk of thromboembolism, caused by an altered blood flow and activation of the coagulation system by exposure of the blood to artificial surfaces [5]. In a systematic review of observational studies major embolism occurred at a rate of 4 per 100 patient-years. This risk was reduced by approximately 75% when patients used a coumarin derivative [6]. Warfarin is more effective in the prevention of thromboembolic events than platelet-inhibitor therapy with aspirin [7]. A combination of a coumarin derivative and an antiplatelet drug has been shown to be even more effective in reducing the risk of death and thromboembolism than a coumarin derivative alone [8].

Venous thromboembolism (deep vein thrombosis or pulmonary embolism) often occurs as a complication after knee or hip replacement surgery [9]. The use of warfarin after discharge from the hospital reduces the risk of this complication [10]. When patients develop a deep vein thrombosis or pulmonary embolism, treatment with an oral anticoagulant is also indicated. Because it takes some time before the normal coagulation factors are cleared from the plasma the effect of coumarin anticoagulants is achieved after a several days. Patients with venous thromboembolism should therefore also start with a low molecular weight heparin for the first few days [11].

CURRENT PRACTICE

Because the dose-response can vary between patients (inter-individual variability) and varies over time within one patient (intra-individual variability), frequent monitoring of the anticoagulant effect is required. This can be done by measuring the prothrombin time expressed as the International Normalised Ratio (INR) [12]. For people not using any anticoagulant, this INR should be 1.0. In most countries, the target INR range for patients with atrial fibrillation or venous thromboembolism is 2.0-3.0, which means that the in vitro coagulation takes 2 to 3 times longer if compared to subjects not using coumarin anticoagulants [13]. For some indications like prosthetic heart valves a higher target range is used (2.5-4.0) [14].

When patients have to initiate coumarin therapy, a standard loading dose is frequently prescribed for the first few days to reach the therapeutic concentration more rapidly. After a few days, the patient´s INR is measured to check the response to the coumarin anticoagulant and the dose is adjusted accordingly. When the patient has reached a stable INR within the target range and a stable dose, on average INR measurements will be repeated every 4-6 weeks.

In most countries treatment with coumarin derivatives is managed by the GP or in the hospital (routine practice). In some countries, for example Spain and the Netherlands, the treatment is managed by specialised anticoagulation

clinics [15,16]. The quality of care, assessed as percentage time spent in the therapeutic range, is higher in anticoagulation clinics than in routine practice. In a systematic review and meta-regression in 2006, the percentage time spent in the therapeutic range was 58% in routine practice and 66% in anticoagulation clinics [17]. In the Netherlands all coumarin users when treated outside the hospital are treated by an anticoagulation clinic and the target range for patients with atrial fibrillation or venous thromboembolism is 2.0-3.5. The percentage time in this range was as high as 80% for patients using long-term anticoagulants in 2011 [18]. Management by anticoagulation clinics has been found to be cost-effective compared to routine practice [19].

Patients using long-term anticoagulant therapy can find it bothersome to visit the clinic often for INR measurement. Many of these patients prefer self-monitoring, which is possible using a finger prick point of care test. When a patient only self-tests, the result is forwarded to the physician who will determine the next coumarin dose. With patient self-management, the patients can also adjust the dose themselves, after sufficient training [20].

CHALLENGES

Coumarin derivatives have a small therapeutic window. When the dose is too low, the risk of thromboembolic events remains high and the drug is not effective. When the dose is too high, the risk of bleeding is increased [21]. Bleeding events are the most frequent serious adverse effects of coumarin derivatives. These events can vary from mild haematoma to life-threatening or fatal intracranial haemorrhage. In addition, there is a large inter-individual and intra-individual variability in dose-response. Therefore, giving patients the right dose is challenging. The daily dose can vary up to 10-fold between patients for warfarin (1.5 to 14 mg) as well as for acenocoumarol (1 to 9 mg) or phenprocoumon (0.75-9 mg) [22]. Coumarin anticoagulant use therefore often results in drug-related hospitalisation [23,24].

Which dose is required for a certain patient depends on several factors. The dose can vary between patients because of differences in, for example, age, height, weight, sex, concomitant medication and comorbidities [25-27]. Older patients generally require a lower dose, taller or heavier patients a higher dose. Genetic factors also play an important role here, and will be discussed in detail later in this review. The required dose can also vary over time within one patient because of changes in concomitant medication, diet or health status (fever, vomiting etc.) [28-30]. Many interactions with other drugs exist because of inhibition or induction of the CYP2C9 enzyme [31]. Adherence changes of coumarins, as in many other drugs, also influence the response to the anticoagulants [32].

PHARMACOKINETICS AND DIFFERENCES BETWEEN COUMARIN ANTICOAGULANTS

In Europe, different coumarin derivatives are used of which warfarin, acenocoumarol, and phenprocoumon are most frequently prescribed [33]. All coumarin derivatives are 4-hydroxycoumarins. Each coumarin anticoagulant has a single, chiral centre with an S- or an R-enantiomeric form. The drugs are administered as racemic mixtures consisting of 50% of each enantiomer [31]. Although the working mechanism of these drugs is similar, there are some important differences in pharmacokinetics between warfarin, acenocoumarol and phenprocoumon.

All coumarin anticoagulants (except S-acenocoumarol) are absorbed from the gastrointestinal tract with almost complete oral bioavailability. S-acenocoumarol undergoes extensive first pass metabolism. Within a few hours, peak plasma concentrations are reached [31]. Approximately 98-99% of the coumarin anticoagulant is bound to plasma albumin [22]. Metabolism into inactive metabolites takes place in the liver by various hydroxylation reactions, catalysed by cytochrome P450 (CYP) enzymes.

S-warfarin (the most active form) is mainly metabolised by CYP2C9. R-warfarin is metabolised by several other CYP isoforms [34]. CYP2C9 is also the principal metabolising enzyme of both acenocoumarol enantiomers, but plays a less important role in phenprocoumon metabolism, where CYP3A4 is also involved [35,36]. Of these three coumarin anticoagulants, phenprocoumon has the longest elimination half-life of 110-130 hours [37]. Warfarin half-life varies from 24-33 hours for S-warfarin to 35-58 for R-warfarin [38]. Acenocoumarol has the shortest half-life. Although the S-enantiomer is more active, the anticoagulation effect of acenocoumarol mainly depends on the R-enantiomer, because of the short half-life of S-acenocoumarol (1.8 hours). The elimination half-life of R-acenocoumarol is 6.6 hours [39].

PHARMACOGENETICS

Genetic variants play an important role in the large variation in dose requirements. Certain polymorphisms in two genes (*CYP2C9* and *VKORC1*) can explain approximately one-third of the dose variation [40,41]. The contribution of *VKORC1* to the variation in dose requirement is larger (approximately 30%) than the contribution of *CYP2C9* (usually less than 10%) [22].

CYP2C9 - PHARMACOKINETICS

Soon after Rettie *et al.* identified CYP2C9 as the main metabolising enzyme of warfarin in 1992 [42], the effect of the *2 polymorphism on the dose requirement was shown [43]. Aithal *et al.* first described that both *2 and *3 allele carriers required a lower dose and had an increased risk of bleeding [44]. Since publication of this study, many others investigated the effect of these polymorphisms on warfarin dose

requirement and other related outcomes (overanticoagulation, bleeding etc.). Table 1 summarises some of the evidence on the association between *CYP2C9* genotypes and coumarin anticoagulant dose or bleeding risk. A meta-analysis of pharmacogenetic studies on warfarin revealed that the reduction in warfarin dose requirement varied from 20% for heterozygous carriers of a *2 allele to 78% in homozygous carriers of a *3 allele compared to wild-types [45]. In the studies measuring bleeding risk, carrying one or more *CYP2C9* variant alleles was associated with an approximate doubling of bleeding risk compared to

the wild-type [46]. Since *CYP2C9* variants influence the pharmacokinetics of coumarin anticoagulant anticoagulants, it is possible that the risk of bleeding in patients carrying a variant allele is not only increased because of the lower dose requirement, but also because of a slower response to changes in dose.

Although less has been published about *CYP2C9* genotypes and acenocoumarol dose than about warfarin, there are several studies confirming the associations found with warfarin, genotypes and bleeding risk for acenocoumarol. The presence of a *CYP2C9* *3 allele reduces the metabolism of the normally clinically

Table 1. Association between *CYP2C9* genotypes and dose or bleeding risk

Reference	Country	n	Study type	Association
Warfarin				
Lindh 2009 [45]	Various	39 studies	Meta-analysis	Dose reduction:*1*2: 20%, *1*3: 34%, *2*2: 36%, *2*3: 57%, *3*3: 78%
Sanderson 2005 [46]	Various	2 or 3 studies	Meta-analysis	Dose reduction *2: 17%, *3: 37% Bleeding risk *2 RR: 1.91, *3 RR: 1.77, *2 or *3: RR 2.26
Acenocoumarol				
Tassies 2002 [49]	Spain	325	Observational	Dose reduction *1*2: 16%, *1*3: 36%, *2*2: 1%, *2*3: 27%
Schalekamp 2004 [47]	The Netherlands	231	Observational	Dose reduction *2: 1%, *3: 20%
Visser 2004 [48]	The Netherlands	1124	Observational	Dose reduction *1*2: 13%, *1*3: 20%, *2*2: 28%, *2*3: 40%
Visser 2004 [51]	The Netherlands	996	Observational	Major bleeding risk variant carriers: HR: 1.83
Phenprocoumon				
Hummers 2003 [54]	Germany	185	Observational	Bleeding risk *2: OR 0.35, *3: OR 3.10
Schalekamp 2004 [53]	The Netherlands	284	Observational	Dose reduction *2: 21%, *3: 25%
Visser 2004 [48]	The Netherlands	1124	Observational	Dose reduction *1*2: 10%, *1*3: 17%, *2*2: 33%. In *2*3 patients (n=3) dose increased by 9%

inactive S-acenocoumarol and thereby increases the half-life of this enantiomer [39]. Mean acenocoumarol dose requirement is therefore 19-29% lower in carriers of this allele than in wild-types [47], but also 13-15% lower in carriers of a *2 allele [48,49]. The risk of overanticoagulation is increased in *3 carriers [47,49,50]. One study found an increased risk of major bleeding which was seen in *2 and *3 carriers with a hazard ratio of 1.83 [51].

Because CYP2C9 is not the principal metabolising enzyme of phenprocoumon, one might expect that it would have a less pronounced effect in the pharmacogenetics of phenprocoumon than for warfarin or acenocoumarol [52]. However, Schalekamp *et al.* found a 22-25% decreased dose requirement in *CYP2C9* variant carriers [53]. In one study, both minor and major bleeding risk was increased (OR 3.10) in *3 carriers [54].

VKORC1 - PHARMACODYNAMICS

In 2004 the gene coding for the target enzyme of coumarin anticoagulant anticoagulants, Vitamin K epoxide reductase complex subunit 1 (VKORC1), was identified [55,56]. Since 2005, many authors have studied the effect of *VKORC1* polymorphisms on warfarin and other coumarin anticoagulant doses. A number of polymorphisms in this gene have been studied. Some rare mutations in *VKORC1* are associated with warfarin resistance [57]. More common are mutations that are associated with insensitivity through altered VKORC1 expression. The -1639G>A, in tight linkage disequilibrium with 1173C>T, is associated with the widest range of variation in gene expression and hence enzyme activity within a number of different populations [58]. In a recent meta-analysis, the difference in warfarin dose in relation to genotype for the -1639 polymorphism was compared for a Caucasian and an Asian population [59]. From their results we could calculate that Caucasian patients with one -1639 A allele required a 25% lower dose and patients with two -1639 A alleles a 50% lower

dose than patients without this variant allele. This effect was also present in Asian patients, although it was smaller (14 and 38% lower doses respectively).

Several authors have shown that acenocoumarol dose is also influenced by *VKORC1* genotype. Reitsma *et al.* already had shown in 2005 that Dutch patients carrying one or two variant alleles for the 1173 polymorphism required a 28% and 47% lower dose, respectively, when compared to wild-types [60]. In Greek acenocoumarol users, heterozygous carriers of a variant allele required a 19% lower dose and homozygous carriers a 63% lower dose [61]. Similar percentages were found in a German and Austrian population (25% and 52%) [62], in a Serbian population (27% and 62%) [63] and amongst Lebanese acenocoumarol users (34% and 50%) [64].

Reitsma *et al.* also investigated the influence of *VKORC1* polymorphism on the phenprocoumon dose. Patients with a CT genotype at position 1173 had a 10% lower dose and patients with a TT genotype a 52% lower dose than wild-types (CC) [60]. This effect was also seen in

several German and Austrian studies. The dose in phenprocoumon users with one variant *VKORC1* allele was 19-31% lower than in wild-type users and 43-51% lower in users with two variant alleles [62,65-67].

Table 2 summarises the current evidence on the association between *VKORC1* genotypes and coumarin anticoagulant dose or bleeding risk. Reitsma showed an increased bleeding risk in carriers of a *VKORC1* T1173 allele. This effect was larger in phenprocoumon (OR 2.6) than in acenocoumarol (OR 1.2) [60]. Although *VKORC1* genotype was associated with overanticoagulation in a study of warfarin users by Wadelius *et al.*, no effect on bleeding risk was found for *VKORC1* polymorphism [40]. In a study by Montes *et al.* the risk of gastrointestinal bleeding was increased in acenocoumarol users carrying a *VKORC1* polymorphism [68]. In a more recent study, the risk of bleeding was also increased in warfarin users with a *VKORC1* variant allele (incidence of 4.9% in AA, 2.3% in AG and 0.47% in GG patients) [69].

Table 2. Association between *VKORC1* genotypes and dose or bleeding risk

Reference	Country	n	Study type	Association
Warfarin				
Wadelius 2009 [40]	Sweden	1496	Observational	Bleeding risk: no difference between *VKORC1* genotypes
Yang 2010 [59]	Various	19 studies	Meta-analysis	Dose reduction: Caucasians: AG: 25%, AA: 50%, Asians: AG: 14%, AA: 38%
Lund 2012 [69]	Scotland	557	Observational	Bleeding incidence: GG 0.47%, AG 2.3%, AA 4.9%
Acenocoumarol				
Reitsma 2005 [60]	The Netherlands	330	Observational	Dose reduction AG: 28%, AA: 47% Bleeding risk: OR 2.6 in variant carriers
Markatos 2008 [61]	Greece	98	Observational	Dose reduction AG: 19%, AA: 63%
Montes 2008 [68]	Spain	266	Observational	Gastro intestinal bleeding risk AG: OR 1.18, AA: OR 1.51
Cadamuro 2010 [62]	Austria	206	Observational	Dose reduction AG: 25%, AA: 52%
Kovac 2010 [63]	Serbia	200	Observational	Dose reduction AG: 27%, AA: 62%
Esmerian 2011 [64]	Lebanon	133	Observational	Dose reduction AG: 34%, AA: 50%
Phenprocoumon				
Reitsma 2005 [60]	The Netherlands	330	Observational	Dose reduction AG: 10%, AA: 52% Bleeding risk: OR 1.2 in variant carriers
Qazim 2009 [66]	Austria	53	Observational	Dose reduction AG: 29%, AA: 49%
Cadamuro 2010 [62]	Austria	206	Observational	Dose reduction AG: 21%, AA: 51%
Puehringer 2010 [65]	Austria and Germany	185	Observational	Dose reduction AG: 19%, AA: 43%
Geisen 2011 [67]	Germany	75	Observational	Dose reduction AG: 31%, AA: 50%

However, this increase in risk was limited to the first month of treatment. An increased risk of overanticoagulation (and thereby indirectly an increased bleeding risk) in *VKORC1* variant carriers was also observed in phenprocoumon (limited to the first month also) and acenocoumarol (limited to the first 3-6 months) users [70,71].

A recent study showed that polymorphisms in VKORC1 -1639G>A also influence the response to acute vitamin K supplementation in over-anticoagulated patients. The INR decreased faster in patients carrying the G allele [72].

OTHER GENES

The association between coumarin anticoagulant dose and other genes besides *CYP2C9* or *VKORC1* has also been investigated. For example, an effect has been found for *GGCX,* encoding the enzyme catalysing the carboxylation of vitamin K dependent clotting factors [73], for *APOE,* encoding the vitamin K liver-uptake facilitating ligand Apolipoprotein E [74], for *PROC,* encoding Protein C, which inactivates clotting factor Va and VIIIa [75], for *CYP4F2,* encoding the CYP enzyme that metabolizes vitamin K [76] and for *GATA-4,* encoding the transcription factor involved in the regulation of *CYP2C9* [77]. However, these effects could not always be replicated, or explained only a very small part of the dose variation.

GENOTYPE-GUIDED DOSING ALGORITHMS FOR WARFARIN

The first dosing algorithms incorporating *CYP2C9* genotype were published in 2004 [78-80]. The algorithm by Gage *et al.* was the most extensive and included, in addition to *CYP2C9* genotype, age, body surface area, sex, race, target INR, amiodarone use and simvastatin use. The algorithm explained 39% of the variation in daily warfarin dose. Since that time, more than 30 algorithms have been published based on both *CYP2C9* and *VKORC1* genotype (Table 3). Sconce *et al.* published one of the first algorithms, including *CYP2C9* and *VKORC1* genotypes as well as age and height [81]. This algorithm explained 54% of the warfarin dose variation in a British population.

CYP2C9 genotype alone explained 17.5% of the variation and *VKORC1* genotype 15%. The algorithm by Carlquist *et al.* was developed in an American population and included *CYP2C9* and *VKORC1* polymorphisms, age, weight and sex ($R^2 = 0.45$) [82]. In 2008, Gage *et al.* published an updated algorithm including *CYP2C9* and *VKORC1* genotype, but also age, body surface area, amiodarone use, target INR, race and smoking status [83]. In a Caucasian population this algorithm explained 57% of the dose variation, but the predictive value was lower (31%) in African-Americans. Wadelius *et al.* were able to explain almost 59% of the variation in a Swedish population, using information

on both genotypes, age, race, sex and the number of interacting drugs capable of increasing the INR [40]. The univariate R^2 of *CYP2C9* genotype was approximately 12% and that of *VKORC1* 29%. The International Warfarin Pharmacogenetics Consortium (IWPC) created an algorithm in a more diverse population from 9 countries in 4 continents [84]. Forty-seven percent of the dose variation was explained by *CYP2C9, VKORC1*, age, height, weight, amiodarone use, race and number of CYP enzyme inducers. An alternative measure to the percentage of variation explained by the algorithm (R^2) is the mean absolute error (MAE), although this is not reported for all algorithms. Table 3 also shows this measure for the studies where this measure was reported.

For warfarin, many more algorithms have been published in different populations from several countries, such as the USA 85, UK and Canada 86,87, Italy 88,89, Slovenia 90, Singapore 91, Japan [92-94], Korea [95,96], China [97-100],
Indonesia [101], India [102], Oman [103], Brazil [104] and Puerto Rico [105]. Most of these studies have included *VKORC1* and *CYP2C9* genotypes, but some have also included *CYP4F2*, *CCCG* and *APOE* genotypes [89,99].

The formulas from these studies made it possible to calculate a warfarin maintenance dose. However, only a handful of studies have looked at algorithms for other types of coumarin anticoagulant doses. Avery *et al.* also described how to derive an initiation dose from an adapted version of the IWPC algorithm [106]. Gong *et al.* reported both a pharmacogenetic loading and maintenance dose in their publication [86]. When a patient initiates warfarin on a pharmacogenetic-guided dose, it is difficult to know how to adjust this dose after INR measurement. In 2010, a dose refinement algorithm was developed in a combined population from the USA, UK, Sweden and Thailand making use of the first INR measurement [107]. Later, the same group published an algorithm using INR information from days 6 to 11 [108].

GENOTYPE-GUIDED DOSING ALGORITHMS FOR ACENOCOUMAROL AND PHENPROCOUMON

Considerably less has been published on pharmacogenetic-guided algorithms for acenocoumarol and phenprocoumon doses compared to warfarin doses (Table 3). Van Schie *et al.* developed a genotype-guided algorithm for both acenocoumarol and phenprocoumon in a Dutch population [27]. The authors also provided loading doses related to the calculated maintenance dose and validated the acenocoumarol algorithm later in a different Dutch population which yielded an R^2 of 52.7% [109]. Other
acenocoumarol algorithms were developed in Greek [61], Indian [110] and Spanish [111,112] populations. For phenprocoumon, only one other study has developed an algorithm [67]. In a small (n=75) German population *VKORC1* genotype, age and weight explained 48.6% of the daily phenprocoumon dose variability. *CYP2C9* genotype was not associated with phenprocoumon dose in this study. In the study by van Schie *et al.* the predictive value of this gene was 4.5%, similar to that of acenocoumarol [27].

Table 3. Published algorithms to predict the required coumarin anticoagulant dose

Reference	Country	n	type	Genetic parameters	Clinical parameters	R^2	MAE (mg/day)
Warfarin							
Gage 2004 [79]	USA	369	M	CYP2C9	age, sex, BSA, race, target INR, CM	39%	-
Hillman 2004 [78]	USA	453	M	CYP2C9	age, BSA, valve replacement, diabetes	34%	-
Kamali 2004 [80]	UK	121	M	CYP2C9	age	20%	-
Sconce 2005 [81]	UK	297	M	CYP2C9, VKORC1	age, height	54%	-
Carlquist 2006 [82]	USA	213	M	CYP2C9, VKORC1	age, sex, weight	45%	-
Herman 2006 [90]	Slovenia	165	M	CYP2C9, VKORC1	age, BSA	60%	-
Takahashi 2006 [92]	Japan	365	M	CYP2C9, VKORC1	age, weight	57%	-
Tham 2006 [91]	Singapore	107	M	CYP2C9, VKORC1	age, weight	60%	-
Gage 2008 [83]	USA	1015	M	CYP2C9, VKORC1	age, BSA, race, target INR, CM, smoking	57%	1.3
Perini 2008 [104]	Brazil	390	M	CYP2C9, VKORC1	age, weight, heart valve prosthesis, thromboembolic disease, CM	50%	0.99
Wu 2008 [85]	USA	92	M	CYP2C9, VKORC1	age, sex, weight, height, race, CM, smoking	59%	-
IWPC 2009 [84]	Various	4043	M	CYP2C9, VKORC1	age, height, weight, race, CM	47%	1.19
Huang 2009 [97]	China	266	M	CYP2C9, VKORC1	age, BSA	45%	-
Sasaki 2009 [93]	Japan	45	M*	CYP2C9, VKORC1	*	94%*	-
Wadelius 2009 [40]	Sweden	1496	M	CYP2C9, VKORC1	age, sex, race, CM	59%	-
Harada 2010 [94]	Japan	97	M	CYP2C9, VKORC1, CYP4F2	age, white blood cell count, CM	49%	-
Lenzini 2010 [107]	Various	969	R	CYP2C9, VKORC1	age, BSA, race, stroke, target INR, diabetes, CM, dose and INR values	60%	0.79
Wells 2010 [87]	Canada	249	M	CYP2C9, VKORC1, CYP4F2	age, BMI, height, exercise level, CM	58%	-
Avery 2011 [106]	UK	671	I	CYP2C9, VKORC1	age, height, weight, CM	42%	-
Cho 2011 [95]	Korea	130	M	CYP2C9, VKORC1	age, BSA, CM	60%	-

Study	Country	N	Dose	Genes	Predictors	%	
Choi 2011 [96]	Korea	564	M	CYP2C9, VKORC1, CYP4F2, GGCX	age, BSA, sex, INR	35%	-
Gong 2011 [86]	UK and Canada	167	I&M	CYP2C9, VKORC1, CYP4F2	age, weight, sex, CM	42%	1.49
Suriapranata 2011 [101]	Indonesia	85	M	CYP2C9, VKORC1	age, weight, height	21%	-
You 2011 [98]	China	100	M	CYP2C9, VKORC1	age, weight, vitamin K intake	68%	-
Zambon 2011 [89]	Italy	274	M	CYP2C9, VKORC1, CYP4F2	age, BSA	65%	0.97
Cini 2012 [88]	Italy	55	M	CYP2C9, VKORC1	age, height, weight, sex, smoking, vegetable intake, indication, diabetes	44%	1.42
Horne 2012 [108]	Various	2022	R	CYP2C9, VKORC1	age, BSA, CM, stroke, target INR, dose and INR values	72%	0.71
Pathare 2012 [103]	Oman	212	M	CYP2C9, VKORC1	age, weight, sex, indication	62%	0.26
Pavani 2012 [102]	India	240	M	CYP2C9, VKORC1	age, BMI, sex, vitamin K intake	89%	-
Ramos 2012 [105]	Puerto Rico	163	M	CYP2C9, VKORC1	age, indication, CM, dose-adjusted INR	67%	0.79
Wei 2012 [99]	China	325	M	CYP2C9, VKORC1, CYP4F2	age, weight, previous thromboembolism, CM	52%	-
Xu 2012 [100]	China	207	R	CYP2C9, VKORC1, CYP4F2	age, BSA, target INR and INR values	54%	0.59
Acenocoumarol							
Markatos 2008 [61]	Greece	98	M	CYP2C9, VKORC1	age, sex, CM	55%	-
Van Schie 2011 [27]	The Netherlands	375	I&M	CYP2C9, VKORC1	age, height, weight, sex, CM	56%	0.52
Borobia 2012 [111]	Spain	147	M	CYP2C9, VKORC1, CYP4F2, APOE	age, BMI, CM	61%	0.52
Rathore 2012 [110]	India	125	M	CYP2C9, VKORC1, CYP4F2, GGCX	age, weight, height, BSA, sex, smoking, indication	41%	0.71
Cerezo-Manchado 2013 [112]	Spain	973	M	CYP2C9, VKORC1, CYP4F2	age, BSA, sex	50%	-
Phenprocoumon							
Van Schie 2011 [27]	The Netherlands	559	I&M	CYP2C9, VKORC1	age, height, weight, sex, CM	53%	0.45
Geisen 2011 [67]	Germany	75	M	VKORC1	age, weight	49%	-

M=Maintenance dose, R=Refinement, I=Initiation dose, CM=concomitant medication, MAE=mean absolute error. *PKPD model

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EVALUATION OF EFFECTIVENESS OF GENOTYPE-GUIDED DOSING

Pharmacogenetic-guided dosing was first evaluated by Voora *et al.* [113]. In this study the safety and feasibility of using the dosing algorithm of Gage *et al.* (2004) [79] was investigated in 48 patients. The authors found that this dosing regimen was feasible and improved the time to stable dose in carriers of a *CYP2C9* variant allele. The risk of supratherapeutic INR values was not decreased in this group. A few months later, the first (pilot) randomised trial in 38 patients was published [114]. These authors drew a similar conclusion, reporting that genotyping seemed to be feasible and acceptable to patients and providers. No differences were found in percentage time in INR range or the risk of supratherapeutic INR values. Another randomised trial with 191 patients also investigated the added value of a dose based on *CYP2C9* genotype and found that the time to stable dose was decreased and the time spent in therapeutic range was increased in the intervention group versus the control group [115].

Anderson *et al.* [116] were the first to investigate the impact of genotyping for both *CYP2C9* and *VKORC1* genotypes, using the algorithm of Carlquist *et al.* [82] and a weighted overview of other observational studies. In this study, 220 patients were included and the patients in the intervention arm required fewer INR measurements and dose adjustments than in the control arm. However, no effect on the number of out-of-range INR values could be demonstrated when looking at all patients. In wild-type patients and patients carrying multiple variant alleles, genotyping decreased the risk of out-of-range INRs by 10%. In a randomised controlled study published in 2009, 121 Chinese patients undergoing heart valve replacement surgery were included [97]. Patients who received a dose based on the genotype-guided algorithm spent more time within the target range and required less time to reach a stable dose than patients receiving a standard dose. In China, the standard initiation dose is 2.5 mg/day. Another Chinese randomised trial using the same algorithm was published in 2012 [117]. The group receiving a loading dose according to this pharmacogenetic algorithm (n=50) reached stable dosing faster than the group receiving a standard loading dose of 2.5 mg/day (n=51).

Several non-randomised prospective studies on pharmacogenetic-guided dosing of warfarin using both *VKORC1* and *CYP2C9* have also been published. Wen *et al.* showed that genotyping for these genes could help to decrease the time to stable dose, although this study did not have a control group [118]. In the study by Lenzini *et al.* the percentage time in therapeutic range was higher in the genetic group and the risk of adverse events lower compared to the clinical control group [119]. McMillin *et al.* [120] compared 2 parallel cohorts, one receiving a standard dose and the other receiving a dose based on the algorithm by Sconce *et al.* [81], and found that the outcomes in the two parallel cohorts were not statistically significantly different. In another study, patients in a historical control cohort were more frequently hospitalized for bleeding or thromboembolism than patients whose genotype was reported to

Table 4. Current evidence on pharmacogenetic-guided dosing of warfarin

Reference	Country	n	Type	Genotypes	Comparator	Effect of genotype-guided dosing
Voora 2005 [113]	USA	48	Prospective cohort	CYP2C9	None	Decreased time to stable dose, no effect on overanticoagulation
Hillman 2005 [114]	USA	38	RCT	CYP2C9	Standard care	No effect on % time in therapeutic range or overanticoagulation
Anderson 2007 [116]	USA	220	RCT	CYP2C9, VKORC1	Standard care	Fewer INR measurements and dose adjustments were required, no overall effect on out-of-range INRs
Caraco 2008 [115]	Israel	191	RCT	CYP2C9	Standard care	Time to stable dose was decreased, time spent in therapeutic range was increased
Wen 2008 [118]	Taiwain	108	Prospective cohort	CYP2C9, VKORC1	None	Decreased time to stable dose
Lenzini 2008 [107]	USA	412	Prospective cohort	CYP2C9, VKORC1	Clinical algorithm	Increased % time in therapeutic range, decreased risk of adverse events
Huang 2009 [97]	China	121	RCT	CYP2C9, VKORC1	Standard care	Decreased time to stable dose, no effect on overanticoagulation, increased % time in therapeutic range
Epstein 2010 [121]	USA	896	Prospective cohort	CYP2C9, VKORC1	Historical cohort	Decreased hospitalisation for bleeding or thromboembolism
McMillin 2010 [120]	USA	229	Prospective cohort	CYP2C9, VKORC1	Standard care	No statistically significant differences
Burmester 2011 [122]	USA	125	RCT	CYP2C9, VKORC1	Clinical algorithm	No differences between the two arms
Gong 2011 [86]	UK and Canada	196	Prospective cohort	CYP2C9, VKORC1	None	Eliminated differences in time to therapeutic INR between the genotypes
Anderson 2012 [123]	USA	504	RCT + parallel cohort	CYP2C9, VKORC1	Different genotype-guided algorithm	Both algorithms increased % time in therapeutic INR range and decreased the number of out-of-range INRs
Wang 2012 [117]	China	101	RCT	CYP2C9, VKORC1	Standard care	Decreased time to stable dose

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the physician [121]. Gong *et al.* found that the differences in time to therapeutic range between genotypes were eliminated when patients were dosed according to a genotype-guided algorithm, but a comparison with a control group was not possible [86].

In a more recent randomised controlled trial by Burmester *et al.*, dosing using a pharmacogenetic algorithm was not compared with standard care, but to a clinical algorithm [122]. In both arms, the initial warfarin doses were closer to the stable therapeutic dose than they would have been on a standard dose of 5 mg/day. No differences between the two arms were found for percentage time in therapeutic range. Also Anderson *et al.* compared two algorithms, but both genotype-guided, and could not find differences between the two groups [123]. But in this study, patients

dosed with any of the two pharmacogenetic algorithms (n=504) spent more time within the target range and had less out-of-range INRs than patients on standard care in a parallel cohort (n=1911). This is the largest study comparing genotype-guided dosing to standard care to date and probably the only one with sufficient statistical power to detect a significant difference between pharmacogenetic-guided care and standard treatment. However, none of the studies described above (and summarised in Table 4) were able to provide convincing evidence about the clinical significance of genotyping, either because of the small size of the study or a non-randomised comparison. Also, no trials have been published yet describing the impact of genotyping before initiating acenocoumarol or phenprocoumon treatment.

STUDIES IN PROGRESS

Some additional clinical trials are currently recruiting patients or have just finished recruiting. In the Clarification of Optimal Anticoagulation through Genetics (COAG) trial, a double blind randomised clinical trial, the percentage time patients spend in the therapeutic INR range during the first 4 weeks of therapy will be investigated in two groups [124]. The first group will receive a genotype-guided dose based on algorithms using clinical and genetic information. The second group will receive a clinical-guided dose based on algorithms using clinical information only. Patients are currently being recruited from several centres in the USA. The Genetics Informatics trail (GIFT) is a 2x2 factorial design trial, comparing a

pharmacogenetic algorithm with a clinical algorithm and a high INR target (2.5) with a lower INR target (1.8) [125]. In this study, patients undergoing hip or knee surgery and receiving prophylactic warfarin are being included. The primary outcome is a composite of venous thromboembolism, major bleeding, INR values above 4 or death. Both the COAG trial and the GIFT trial aim to include more than 1000 patients. All aforementioned trials have focused on warfarin. Carcas *et al.* described the study protocol of a trial on acenocoumarol [126]. In this Spanish multicentre, single blind, randomised trial, 240 patients with venous thromboembolism will be included and followed for three months. Patients in the control group will be dosed according

to common clinical practice; patients in the intervention group will be dosed according to the algorithm of Borobia *et al.* [111]. The primary endpoint is whether or not the INR at day 7 of acenocoumarol therapy is in the therapeutic range.

The European pharmacogenetics of anticoagulant therapy (EU-PACT) trial is a European trial investigating the added value of genotyping in warfarin, acenocoumarol and phenprocoumon [127]. This trial includes patients with atrial fibrillation or venous thromboembolism initiating warfarin (in the UK and Sweden), acenocoumarol (in Greece and The Netherlands) or phenprocoumon (in The Netherlands, Austria and Germany). Patients are being randomised to either an intervention group or a control group. The acenocoumarol and phenprocoumon control group will receive a dose based on a clinical algorithm; the warfarin control group will receive a dose based on standardised clinical care. The dosing algorithms by van Schie *et al.* and by Avery *et al.* are used to calculate loading and maintenance doses [27,106]. The primary outcome of this trial is the percentage time in therapeutic INR range during the first three months of therapy. Secondary endpoints include percentage time spent with INR of 4 or higher, time to stable dose, time to therapeutic INR, time to and number of adverse events (bleeding or thromboembolism) and cost-effectiveness. A new method will be used to genotype patients for *CYP2C9* and *VKORC1* polymorphisms [128]. This method is a point-of-care test, providing the results in approximately 1.5 h. This enables physicians to prescribe a pharmacogenetic-guided dose before treatment initiation without delaying the start of the therapy.

COST-EFFECTIVENESS

If and when pharmacogenetic-guided coumarin dosing has been shown to be effective and safe, clinical practice guidelines will probably recommend genotyping. But widespread implementation of the dosing strategy will also depend on its cost-effectiveness. The payer, for example a health insurance company, is an important stakeholder in this case. If the genetic test is not reimbursed, patients might not be willing or able to undergo this test and receive a genotype-guided dose. The insurance company may require proper information from cost-effectiveness analyses before considering reimbursement.

A cost-effectiveness analysis (CEA) involves the comparison of the total costs and effectiveness of two or more different treatment strategies. In such an analysis different costs are considered, including not only the costs of genotyping and the cost of monitoring, but also the costs of cardiovascular events that may occur later in time. The effectiveness of genotyping can be defined in different ways. It can be oriented around the reduction in adverse events, in which case the cost-effectiveness of genotype-guided dosing versus clinical-guided (or standard) dosing will be expressed as the extra cost to avoid one adverse event. This is, however, very disease-specific and therefore difficult to compare with treatments in other diseases. For a health insurance company

comparability with other treatments may be very valuable when making 'value for money' or budget allocation decisions. For this reason, some payers require a cost-utility analysis (CUA), where the utility of the new treatment is usually expressed in Quality Adjusted Life Years (QALYs). The costs per QALY gained can be compared more easily with treatments in other diseases than the cost per adverse event avoided. Some authors have already investigated the cost per QALY gained by genotype-guided warfarin dosing, but there is still large uncertainty about the effectiveness of a pharmacogenetic-guided algorithm [129,130]. In the EU-PACT trial, the cost per QALY gained by pharmacogenetic guided dosing will be determined for warfarin, acenocoumarol and phenprocoumon [127]. The costs of genotyping will have an important effect on cost-effectiveness. If the costs are low, genotyping could reduce overall costs if the rate of adverse events is decreased.

CONCLUSIONS

Genetic factors play an important role in the response to coumarin derivatives. Dosing algorithms including *CYP2C9* and *VKORC1* genotypes and some clinical factors are able to explain more than half of the variation in coumarin dose requirements. A higher R^2 of the algorithms than what has been found so far, is not expected when more polymorphisms are added, as *CYP2C9* and *VKORC1* (and to a smaller extent *CYP4F2*) are consistently found as the most important determinants of coumarin dose in genome wide association studies [131-134]. The algorithms can be used in clinical practice to predict the right coumarin dose before treatment initiation. The effectiveness of this pharmacogenetic-guided dosing is still uncertain. Currently, novel oral anticoagulants (direct thrombin inhibitors and factor Xa inhibitors) have been developed, which might be good alternatives to coumarin derivatives. A meta-analysis of 5 large phase III trials revealed that these novel oral anticoagulants compared to coumarin anticoagulants reduced the risk of stroke or systemic embolism by 18% and the risk of haemorrhagic stroke by as much as 49% in patients with atrial fibrillation [135]. These results indicate that these drugs are a promising alternative to coumarin derivatives, especially because patients will not have to be monitored frequently, as is the case with coumarin derivatives. However, these novel oral anticoagulants also have some disadvantages. No biomarker is currently available to monitor the anticoagulant effect of the new drugs. This fact, together with the fact that some of the new drugs have to be taken twice daily, could reduce patient adherence. Secondly, in elderly patients with renal dysfunction, the risk of bleeding is increased because of prolonged half-lives in patients with renal insufficiency [136]. In case of a bleed or if emergency surgery is needed, there is no antidote available yet. However, some studies have been done in healthy volunteers, suggesting Prothrombin Complex Concentrate as a possible antidote [137,138]. Lastly, the

costs of novel oral anticoagulants are considerably higher than the costs of coumarin anticoagulants. The costs of the drugs represent only one part of the costs; one needs to consider the monitoring costs and complication costs etc. also. It is therefore also necessary to investigate the cost-effectiveness of these drugs. Shah *et al.* showed that a direct thrombin inhibitor was less cost-effective versus warfarin when patients spent more time within the therapeutic range [139]. As pharmacogenetic-guided dosing may increase the time spent within therapeutic range, it would also be very interesting to investigate the cost-effectiveness of the novel oral anticoagulants versus pharmacogenetic-guided dosing of coumarin derivatives. In a cost-utility analysis, You *et al.* concluded that the chance that pharmacogenetic-guided coumarin dosing would be cost-effective would be high if the time spent in therapeutic INR range could

be improved from 64% to 77% [140]. The new oral anticoagulants are expected to be used more widely in the coming years. This might influence the role of anticoagulation clinics when these clinics have fewer patients to treat. This can increase the operating costs per patient and also influence the cost-effectiveness of pharmacogenetic-guided dosing.

In conclusion, pharmacogenetics play an important role in the interindividual and intra-individual variation in response to coumarin derivatives. Pharmacogenetic-guided dosing algorithms could be used to predict the required coumarin dose before treatment initiation, but the best evidence of the effectiveness of genotype-guided dosing is still forthcoming. After the clinical effect of genotyping is known, it will be important to consider the cost-effectiveness of genotype-guided coumarin dosing, also when comparing to the new oral anticoagulants.

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PART I
DETERMINANTS OF VARIATION IN RESPONSE TO COUMARIN ANTICOAGULANTS

LONG-TERM ANTICOAGULANT EFFECTS OF THE *CYP2C9* AND *VKORC1* GENOTYPES IN ACENOCOUMAROL USERS

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ABSTRACT

Background: The required acenocoumarol dose and the risk of underanticoagulation and overanticoagulation are associated with the *CYP2C9* and *VKORC1* genotypes. However, the duration of the effects of these genes on anticoagulation is not yet known.

Objectives: In the present study, the effects of these polymorphisms on the risk of underanticoagulation and overanticoagulation over time after the start of acenocoumarol were investigated.

Methods: In three cohorts, we analysed the relationship between the *CYP2C9* and *VKORC1* genotypes and the incidence of subtherapeutic or supratherapeutic International Normalised Ratio (INR) values (< 2 and > 3.5) or severe overanticoagulation (INR > 6) for different time periods after treatment initiation.

Results: Patients with polymorphisms in *CYP2C9* and *VKORC1* had a higher risk of overanticoagulation (up to 74%) and a lower risk of underanticoagulation (down to 45%) in the first month of treatment with acenocoumarol, but this effect diminished after 1–6 months.

Conclusions: Knowledge of the patient's genotype therefore might assist physicians to adjust doses in the first month(s) of therapy.

INTRODUCTION

Coumarin derivatives, such as acenocoumarol, phenprocoumon and warfarin, are widely used oral anticoagulants. These drugs are prescribed for the treatment and prevention of thromboembolic events in patients with, for example, venous thromboembolism or atrial fibrillation[1]. Because of the narrow therapeutic window of these drugs, patients need to be monitored frequently by measuring the prothrombin time, expressed as the International Normalised Ratio (INR). A large variability in dose-response exists among coumarin users, which is caused by several factors such as age, concomitant medication and diet, but genetic factors also play an important role[2-6]. Approximately one-third of the variation in coumarin dose requirements can be explained by polymorphisms in the *CYP2C9* gene, encoding for the main metabolizing enzyme, cytochrome P450 2C9 (CYP2C9), and the *VKORC1* gene, encoding for the target enzyme Vitamin K epoxide reductase multiprotein complex 1 (VKORC1)[6-9]. Carriers of a *CYP2C9* *2 or *3 or a *VKORC1* T-allele require a lower coumarin maintenance dose compared with wild-type patients (*CYP2C9* *1*1, *VKORC1* CC)[7,10]. These patients often receive a supratherapeutic dose at the start of treatment, which may lead to overanticoagulation. Lower dose requirements, an increased risk of overanticoagulation in the first month(s) of therapy and delayed stabilization have been shown in carriers of a variant allele in *CYP2C9* and/or *VKORC1* in several studies[11-17]. Moreover, the risk of haemorrhagic adverse events increases with an increased INR. Severe overanticoagulated patients (INR > 6) therefore have a considerably increased risk of a bleeding event[18,19]. However, when

the INR is below the therapeutic range, coumarin therapy is less effective, with a higher risk of (recurrent) thromboembolic events[20]. When physicians are unaware of the genotype of patients, it is conceivable that patients with wild-type genotypes are more often underanticoagulated than variant allele carriers and the latter group has a higher risk for overanticoagulation than the former group. This difference in dose requirements led to the hypothesis that *CYP2C9* and *VKORC1* wild-type patients have an increased risk of subtherapeutic INR values and that carriers of a variant allele have an increased risk of supratherapeutic INR values. Meckley et al.[21] showed an increased risk of overanticoagulation in *CYP2C9* variant carriers in the first 6 months and in *VKORC1* variant carriers in the first month of warfarin treatment. In several European countries, including the Netherlands, acenocoumarol or phenprocoumon are prescribed more frequently for anticoagulant therapy[22]. Schalekamp et al.[15,16] showed an

increased risk of severe overanticoagulation in carriers of a *CYP2C9* or *VKORC1* polymorphism during the first 6 months of acenocoumarol and phenprocoumon treatment. In these previous studies, the first 6 months were not analysed separately, but as a whole. Teichert et al.[17] showed an increased risk of severe overanticoagulation for *VKORC1* variant alleles after an initial standard dose of acenocoumarol treatment.

Whether carriers of a *CYP2C9* or *VKORC1* polymorphism only have an increased risk of overanticoagulation in the first month of therapy or whether this effect is also seen after the initiation period is still unknown, as well as the possible risk of underanticoagulation in wild-type patients. The aim of the present study was therefore to investigate the association of the *CYP2C9* and *VKORC1* polymorphisms with the risk of over and underanticoagulation after the initiation period of acenocoumarol.

METHODS

Study population

For the present study, we looked at data from three different studies. First, data from the pre-EU-PACT study were used[23]. In this cohort study, patients who were using acenocoumarol in November 2009 with a target International Normalised Ratio (INR) in the lowest intensity category (according to Dutch guidelines INR 2.0–3.5) were included. Schalekamp prospectively followed patients newly starting on acenocoumarol with a target INR in the lowest intensity category (2.0–3.5) for 6 months[15]. In this dataset we

therefore could repeat the analyses for the first half year of treatment. In the Rotterdam study, patients on acenocoumarol were followed for their entire treatment period regardless of their target INR[24]. We selected only the patients with a target INR of 2.0 to 3.5 for the present analyses.

The study protocols of the three studies were approved by the Medical Ethics Committee (Leiden University Medical Center, Leiden for pre-EU-PACT, Utrecht Medical Centre, Utrecht for the study of Schalekamp, and Erasmus Medical Center, Rotterdam for the Rotterdam study) and

patients provided informed consent before inclusion into the study. All procedures were conducted in accordance with the Helsinki Declaration.

The data of the three studies were combined to increase the power of the analyses. For the first 6 months, this dataset contains data from all three studies, but for the periods after 6 months only data from Pre-EU-PACT and the Rotterdam study were included.

Data collection

For each participating patient, data on age and gender were obtained from the electronic registry databases of the anticoagulation clinics. INR measurements, prescribed doses and relevant co-medication have been routinely collected and recorded in registry databases at each visit to the anticoagulation clinic in the Netherlands since 1983. Therefore, it was possible to obtain this information for each patient. Patients were genotyped for *CYP2C9*2* (rs1799853), *CYP2C9*3* (rs1057910) and *VKORC1* 1173C>T (rs9934438). In the Pre-EU-PACT study and the Rotterdam study, also data on height and weight were available. More details on the three studies can be found elsewhere[15,17,23].

Statistical analyses

As the target INR for the participants was in the lowest intensity category (INR 2.0–3.5), subtherapeutic INR values were defined as INR < 2 and supratherapeutic INR values as INR > 3.5. As the risk of bleeding events is considerably increased in severe overanticoagulated patients, we also investigated the occurrence of INR values > 6[18,19]. In several time periods up

to one and a half years after treatment initiation, the occurrence of at least one INR < 2, > 3.5 or > 6.0 was studied. When patients reach a stable dose, they require less frequent monitoring than before they were stable. Consequently, the mean number of INR measurements decreases over time. The time periods used in the present study were chosen so as to have a sufficient number of INR measurements in every period. Data from a patient were only included in the analysis of a specific period, if the patient was using the coumarin under study for this entire period. Data on the start of treatment were required for all included patients and follow-up started at the first week of acenocoumarol use.

The difference in risk of at least one INR < 2, > 3.5 or > 6.0 between the different *CYP2C9* and *VKORC1* genotypes was tested with a chi-square test. If the expected number of observations in a cell was below 5, Fisher's exact test was used. Patients with missing data were excluded from the analyses where this data was needed. Because the frequency of homozygous carriers of a variant *CYP2C9* allele is low, the *CYP2C9* genotype was grouped to increase the group sizes for our analyses. We grouped the *2 carriers together (*1*2 and *2*2) and the *3 carriers together (*1*3, *2*3 and *3*3). The combined effect of *CYP2C9* and *VKORC1* was also investigated for the first month of acenocoumarol use, by combining the two genotypes in six groups, with every *VKORC1* genotype divided into *CYP2C9* wild-type patients and *CYP2C9* variant carriers.

In addition to the occurrence of at least one out-of-range INR during

the different periods, we also looked at the time within, below and above the therapeutic range. This method is more robust for the difference in number of INR measurements between patients. All analyses were performed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient characteristics

In total, 1586 acenocoumarol users from the three studies[15,23,25] were eligible for analyses in the present study. A flowchart of the selection of patients can be found in the Supplement (Figures S1A–C). From the 471 acenocoumarol users in the pre-EU-PACT cohort[23], 231 in the study of Schalekamp[15] and 2065 in the Rotterdam study[25], 275, 192 and 1119 patients were included in the present study. Patient characteristics and genotypes of all 1586 patients are shown in Table 1. Characteristics per study can be found in the Supplement (Tables S1–S3). Data on height and weight were only available in two studies (Pre-EU-PACT and the Rotterdam study). Mean age stratified by genotype varied between 73 and 75 years and 38% to 42% of the participants were male. The most frequent indication for acenocoumarol treatment was atrial fibrillation. The treatment duration at the moment of data collection ranged from 0 to 189 months.

A *VKORC1* CC genotype was seen in 499 patients, a CT genotype in 696 patients and 211 patients had a TT genotype. When the *CYP2C9* genotype was grouped as wild type, *2 carriers and *3 carriers, the group sizes were 938, 312 and 170, respectively. All genotypes were in Hardy–Weinberg equilibrium.

Time periods

The following time periods were considered to ensure a sufficient number of INR measurements in every period: 0–1 month (day 1–30), 1–3 months (day 31–90), 3–6 months (day 91–180), 6–9 months (day 181–270), 9–12 months (day 271–360), 12–15 months (day 361–450) and 15–18 months (day 451–540) after treatment initiation. The average number of INR measurements ranged from 4.6 to 6 for all periods. The INR of carriers of a *VKORC1* variant allele was measured less frequently during months 1–3 and 3–6 than the INR of wild-type patients (P = 0.03 and P = 0.004, respectively, see Table 1).

Because the treatment duration at the moment of data collection was different among the patients, the number of patients decreased over time to 414 acenocoumarol users in the last period (15–18 months, Table 1). Only data of patients using acenocoumarol during the entire period were included in the analysis of a specific period. The maximum follow-up in the study of Schalekamp study was 6 months. The distribution of the different genotypes remained similar in the different time periods.

Subtherapeutic INR values

Figure 1 depicts the occurrence of at least one INR < 2 over the different periods in acenocoumarol users with the different *VKORC1* and *CYP2C9* genotypes. Figure

Table 1. Characteristics of included acenocoumarol users

Patients in study population (n = 1586)	VKORC1				CYP2C9			
	CC	CT	TT		Wild-type	*2 carriers	*3 carriers	
	n= 499	n= 696	n= 211	missing: 180	n= 938	n= 312	n= 170	missing: 166
Male	199 (40%)	286 (41%)	87 (41%)	p= 0.90	388 (41%)	118 (38%)	72 (42%)	p= 0.49
Mean age, years (median)	74 (75)	75 (76)	73 (75)	p= 0.06	75 (76)	75 (76)	73 (74)	p= 0.15
Mean height, cm (median)	168 (167)	168 (167)	168 (168)	p= 0.93	168 (167)	168 (168)	169 (168)	p= 0.30
Mean weight, kg (median)	76 (74)	76 (75)	76 (76)	p= 0.95	76 (75)	76 (74)	77 (78)	p= 0.43
Mean treatment duration, months (median)	15.5 (5.8)	17.4 (5.6)	16.6 (5.3)	p= 0.65	16.6 (5.5)	15.2 (5.2)	17.3 (6.1)	p= 0.38
Amiodaron users	16 (3%)	13 (2%)	3 (1%)	p= 0.21	20 (2%)	7 (2%)	6 (4%)	p= 0.54
Indication for coumarin therapy								
Atrial fibrillation	243 (49%)	332 (48%)	97 (46%)	p= 0.80	445 (47%)	141 (45%)	88 (52%)	p= 0.39
Venous thromboembolism	81 (16%)	97 (14%)	40 (19%)	p= 0.18	136 (15%)	52 (17%)	33 (19%)	p= 0.22
Other	174 (35%)	267 (38%)	74 (35%)	p= 0.41	357 (38%)	118 (38%)	49 (29%)	p= 0.07
Number of INR measurements								
0 – 1 month (n=1484)	5.22	5.10	5.00	p= 0.13	5.14	5.14	5.06	p= 0.64
1 – 3 months (n=1028)	5.03	4.80	4.59	**p= 0.03**	4.88	4.77	4.83	p= 0.79
3 – 6 months (n=786)	5.98	5.47	5.74	**p= 0.004**	5.77	5.50	5.56	p= 0.18
6 – 9 months (n=541)	5.49	5.50	5.35	p= 0.86	5.35	5.68	5.71	p= 0.10
9 – 12 months (n=489)	5.34	5.39	5.81	p= 0.33	5.32	5.59	5.82	p= 0.17
12 – 15 months (n=443)	5.30	4.95	5.14	p= 0.53	5.08	5.29	4.71	p= 0.27
15 – 18 months (n=414)	5.31	5.35	5.37	p= 0.89	5.35	5.41	5.19	p= 0.95

INR= International Normalised Ratio. Bold values indicate statistical significance (P < 0.05).

3

1A illustrates that during the first month, 73% (95% confidence interval [CI]: 68%–77%) of acenocoumarol users with a *VKORC1*-CC genotype had at least one INR measurement < 2. This number was significantly lower among patients with a CT genotype (62%, P < 0.001, 95% CI: 58%–66%) and with a TT genotype (45%, P <0.001, 95% CI: 38%–52%). During months 2–3, the risk of a subtherapeutic INR was 49% (95% CI: 43%–54%) in CC patients, vs. 40% (95% CI: 36%–45%, P = 0.01) and 39% (95% CI: 30%–48%, P = 0.05) in CT and TT patients, respectively. Differences between the *VKORC1* genotypes were not significant after the third month of acenocoumarol use. *CYP2C9* wild-type patients had a 65% (95% CI: 62%–68%) risk of an INR < 2 in the first month, vs. 64% (95% CI: 58%–69%, P = 0.27) and 54% (95% CI: 46%–62%, P = 0.005) in *2 and *3 carriers, respectively. After the first month, no significant differences were found for *CYP2C9* (Figure 1B).

A: Subtherapeutic INR and *VKORC1* genotypes

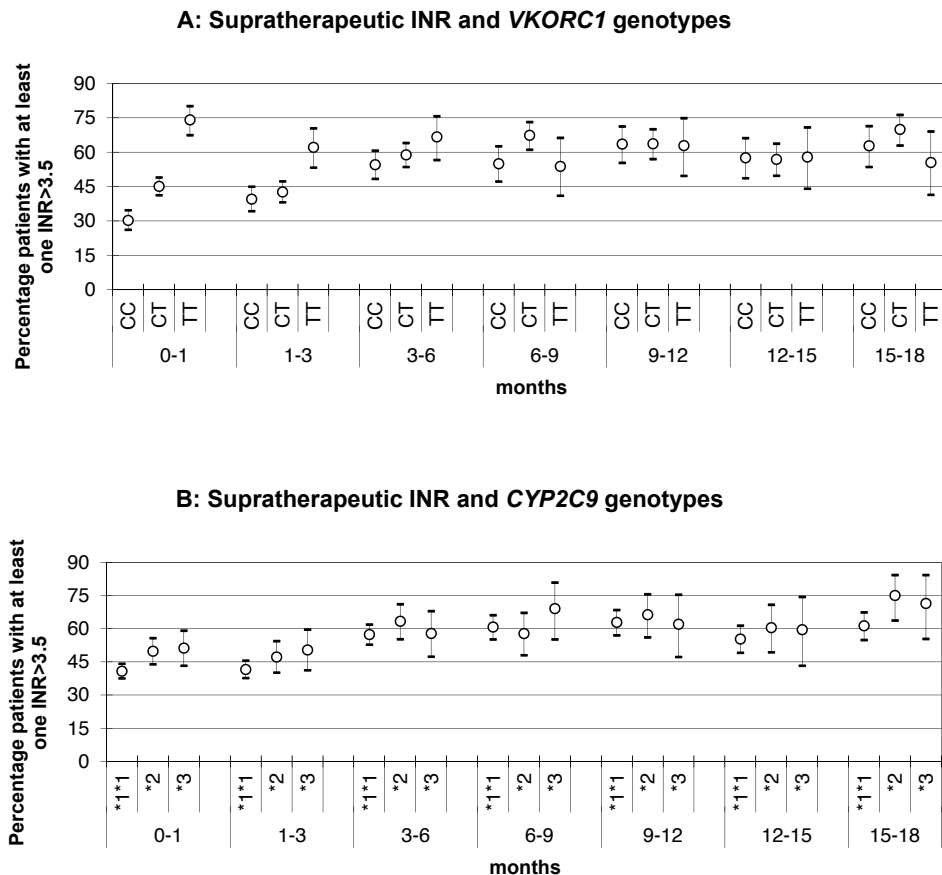### B: Subtherapeutic INR and *CYP2C9* genotypes
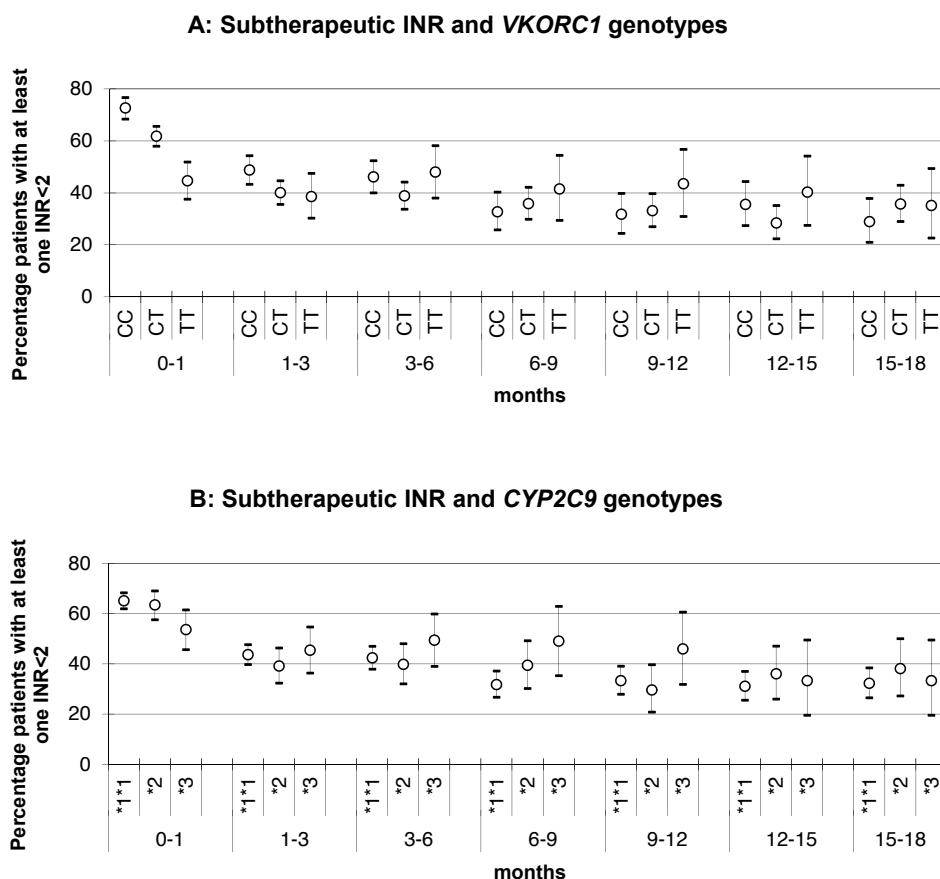
Figure 1. Percentage of patients (and 95% confidence intervals) with at least one International Normalised Ratio (INR) < 2 in the different time periods after coumarin initiation. A: *VKORC1* genotypes B: *CYP2C9* genotypes.

Supratherapeutic INR values

Figure 2 displays the occurrence of at least one INR > 3.5 over the different periods in acenocoumarol users with the different *VKORC1* and *CYP2C9* genotypes. A significant difference between the *VKORC1* genotypes was found up to the third month (Figure 2A). In the first month, supratherapeutic INR values occurred in 30% (95% CI: 26%–35%) of the wild-type patients, vs. 45% (95% CI: 41%–49%, P < 0.001) and 74% (95% CI: 67%–80%, P < 0.001) in patients with a CT and TT genotype, respectively. This difference was smaller (40% (95% CI: 34%–45%)) for wild-type patients, vs. 43% (95% CI: 38%–47%, P = 0.37) for CT and 62% (95% CI: 53%–70%, P < 0.001) for TT in months 1–3. *CYP2C9* wild-type patients had a 41% (95% CI: 38%–44%) risk of an INR > 3.5 in the first month, vs. 50% (95% CI: 44%–56%, P = 0.008) and 51% (95% CI: 43%–59%, P = 0.01) in *2 and *3 carriers, respectively. No significant differences were

A: Supratherapeutic INR and *VKORC1* genotypes

B: Supratherapeutic INR and *CYP2C9* genotypes

Figure 2. Percentage of patients (and 95% confidence intervals) with at least one International Normalised Ratio INR > 3.5 in the different time periods after coumarin initiation. A: *VKORC1* genotypes B: *CYP2C9* genotypes

found between the *CYP2C9* genotypes of acenocoumarol users after the first month (Figure 2B).

Severe overanticoagulation

The risk of severe overanticoagulation (INR > 6) in acenocoumarol users with the different *VKORC1* and *CYP2C9* genotypes is shown in Figure 3 over the different periods. In the first month, 3% (95% CI: 2%–5%) of the *VKORC1* wild-type patients had an INR > 6, vs. 5% (95% CI: 3%–7%, P = 0.26) and 12% (95% CI: 8%–17%, P < 0.001) in CT and TT patients, respectively. In all, 4% (95% CI: 3%–6%) of the *CYP2C9* wild-type patients had an INR > 6 in the first month, vs. 7% (95% CI: 4%–10%, P = 0.07) of the *2 carriers and 9% (95% CI: 5%–14%, P = 0.01) of the *3 carriers. No significant differences were found between the *VKORC1* and *CYP2C9* genotypes after the first month (Figure 3A,B).

A: Severe overanticoagulation and *VKORC1* genotypes
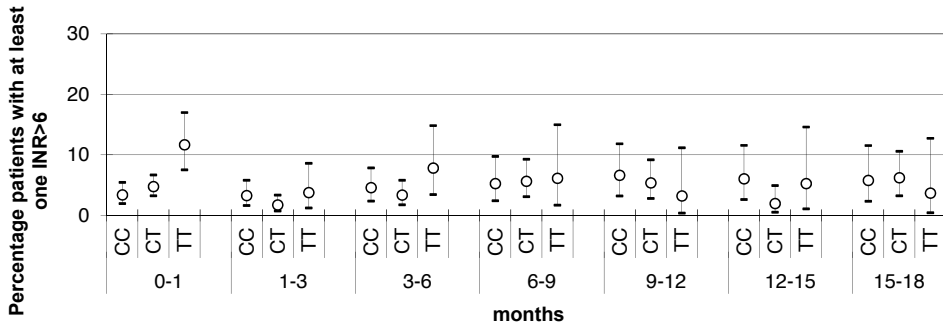
B: Severe overanticoagulation and *CYP2C9* genotypes
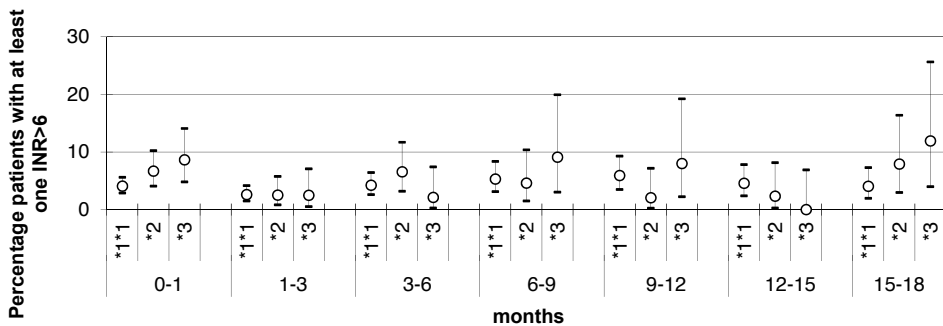
Figure 3. Percentage of patients (and 95% confidence intervals) with at least one International Normalised Ratio INR > 6 in the different time periods after coumarin initiation. A: *VKORC1* genotypes B: *CYP2C9* genotypes.
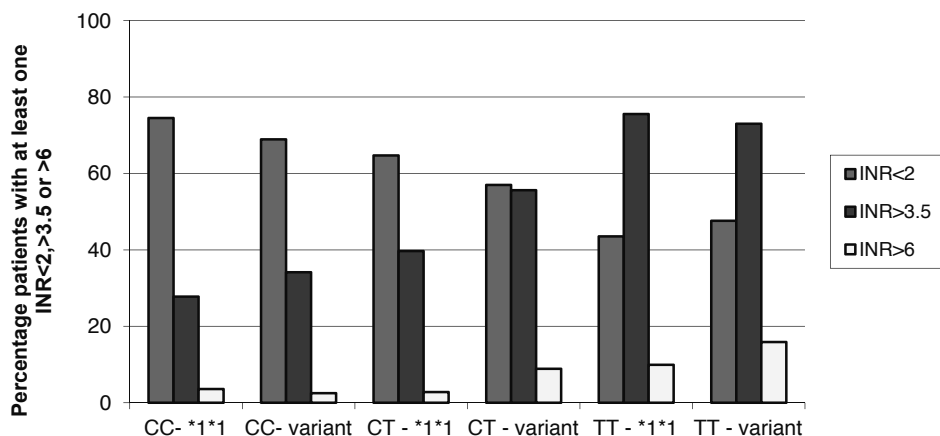
VKORC1 and CYP2C9 genotypes combined

Figure 4 shows the risk of under- and overanticoagulation in the first month for the different combined genotype groups. The risk of underdosing in the first month was greatest (75%, 95% CI: 69%–79%) in *VKORC1* and *CYP2C9* wild-type patients. This risk decreased for every variant allele, with the lowest risk (44%, 95% CI: 35%–52%) existing in *VKORC1* TT and *CYP2C9* wild-type patients. The risk of overdosing increased as the number of variant alleles increased (28% [95% CI: 23%–33%] in *VKORC1* and *CYP2C9* wild-type patients to 76% [95%CI: 67%–83%] in *VKORC1* TT and *CYP2C9* wild-type patients). Severe overanticoagulation in the first month of acenocoumarol use was relatively rare in *VKORC1* CC patients and in VKORC CT/*CYP2C9* wild-type patients (2%–4%) and higher in *VKORC1* CT/*CYP2C9* variant carriers and *VKORC1* TT patients (9%–16%).

Analyses per subcohort

The present analyses of the combined dataset were also performed in the three separate studies. The results of these analyses were similar to the results in the combined dataset and can be found in the Supplement. Only some small differences in results were seen. In the pre-EU-PACT dataset, the risk of underanticoagulation was higher than in the other two datasets (Figures S2 and S3). In this dataset, a significantly different risk of an INR > 3.5 between the *VKORC1* genotypes could be demonstrated up to month 6 (Figure S4). The risk of severe overanticoagulation was relatively low (mostly below 10%) and the confidence intervals in the datasets of pre-EU-PACT and Schalekamp in these analyses were large. Therefore only in the Rotterdam dataset could the effect of *VKORC1* on the occurrence of an INR > 6 be demonstrated, although this trend was also seen in the other datasets (Figure S6).

The results of the analyses on time within, below and above the therapeutic

Figure 4. Risk of under- or overanticoagulation during the first month of coumarin treatment and combined *VKORC1/ CYP2C9* genotypes.

INR range were very similar to the results described above. In the first month, time below the therapeutic INR range was highest in *VKORC1* and *CYP2C9* wild-type patients (up to 31%) and the time above therapeutic INR range was highest in *VKORC1* TT and *CYP2C9* *3 carriers (up to 30%). For *CYP2C9* no difference was found after the first month, but the effect of *VKORC1* on time below the therapeutic INR range lasted up to months 1–3 and on time above the therapeutic INR range up to months 3–6.

DISCUSSION

The present study demonstrates that in the first month of acenocoumarol therapy, the risk of underdosing is highest in patients with a *VKORC1* wild type. This increased risk of a subtherapeutic INR was also seen in months 2 and 3, but not after the third month of coumarin treatment. In addition, the risk of overdosing was highest in patients with a *VKORC1* TT genotype in the first 6 months. For severe overanticoagulation an effect of *VKORC1* was only seen in the first month. After the sixth month, no effect of polymorphisms in *VKORC1* on the occurrence of out-of-range INRs was found.

The effect of the *CYP2C9* genotype on under or overdosing was smaller than the effect of *VKORC1*. Only when we combined three datasets together was a significant difference in the occurrence of subtherapeutic INR values, supratherapeutic values and severe overanticoagulation found between the wild- type patients and the *2 and *3 carriers. However, this effect was only found in the first month of therapy and not after the initiation period.

An increased risk of overanticoagulation among warfarin users with a *CYP2C9* or *VKORC1* polymorphism during the initiation period was also found in the previous study of Limdi et al.[26]. They found that patients with a variant allele had a higher risk of an INR above 4 during the first 30 days. In the present study, we found a larger influence of *VKORC1* than of *CYP2C9*. This difference was also seen in the previous study of Schwarz et al.,[27] who demonstrated that the initial variability in INR response to warfarin was more strongly associated with *VKORC1* than with *CYP2C9*. However, none of these studies investigated the effect of genetic variation on the risk of overanticoagulation after the first month. We found no effect of *CYP2C9* after the first month, but for *VKORC1* we demonstrated an increased risk of overanticoagulation among variant carriers up to 6 months after treatment initiation.

The aforementioned studies focused on the risk of (severe) overanticoagulation, but not on the risk of underanticoagulation. We found an increased risk of a subtherapeutic INR in *CYP2C9* wild-type patients during the first month and in *VKORC1* wild-type patients during the first 3 months. If physicians fear to prescribe high doses, because of uncertainty whether the patient is sensitive or not, frequent underdosing of *VKORC1* and *CYP2C9* wild-type patients is to be

expected. For these patients, the standard dose is often not high enough. The dose will then be adjusted after a couple of INR measurements, mainly during the first weeks of coumarin therapy. Our results thus correspond with these expectations. Patients with venous thromboembolism are often also treated with a low-molecular-weight heparin (LMWH) during the first days, until an INR > 2 is obtained. For these patients the risk of a subtherapeutic INR is compensated by this LMWH during this period. This is not the case for patients with other indications, as for example atrial fibrillation.

Because the Pre-EU-PACT study selected patients using acenocoumarol in November 2009, patients in this cohort did not all have the same length of follow-up. At the time of data collection, some patients were already using acenocoumarol for years, whereas others had just started using acenocoumarol. This is a limitation to the present study, not only because of the lower numbers of patients in the later periods, but also because we might have missed very unstable patients. These patients often stop using acenocoumarol early and therefore might be underrepresented in this cohort. However, we do not believe this had a large influence on our results because the results in the pre-EU-PACT study were very similar to the results in the other studies and the follow-up time was not different among the different genotypes (Table 1). We also performed a survival analysis using the prospective data of Schalekamp, and we found no differences in loss to follow-up between the genotypes. Of the 192 patients included from this cohort, four patients (2%) stopped within the first month.

Patients in the three Dutch cohorts were treated with a therapeutic INR range of 2.0–3.5. This is standard care in the Netherlands, but differs from other countries where normally a range of 2.0–3.0 is used. In the present study, we therefore defined supratherapeutic INR values as INR > 3.5. As we used this as a marker of instability and we obtained similar results in our analysis on time above therapeutic range, we believe our results are also relevant for other countries.

A difference in risk of out-of-range INRs was found between the three studies. The data have been collected in different clinics, and as clinics perform differently, this can explain this variation. However, the effect of the different genotypes and the trend over time remains similar across the different clinics/datasets. Because data from different clinics were used, we believe our study population reflects the Dutch population well.

The likelihood of a patient having an out-of-range INR value depends on how often the INR is checked. This could influence the results when we use occurrence of at least one INR below or above a certain value. In the Netherlands, patients are monitored frequently (on average 21 times per year), especially in the first year. However, we also studied the effect of the genotypes on the percentage time within, below and above the therapeutic INR range, and these analyses yielded similar results. Using this metric (% of time), the results are relatively robust for the frequency of INR monitoring.

Although we did not find an effect of being a carrier of *CYP2C9* or *VKORC1* polymorphisms after the sixth month of

therapy, for *VKORC1* we did find an effect on subtherapeutic and supratherapeutic INR values after the first month. This could mean that knowledge of the patient's genotype could help to determine dose adjustments for acenocoumarol users. This might be useful if the patient has an out-of-range INR. In this case, carriers of a variant allele could be treated with smaller dose adjustments than wild-type patients. This would not only be useful for the sensitive patients to prevent supratherapeutic INR values and thereby decrease the risk of bleeding, but also for wild-type patients. In the present study, we have shown an increased risk of underdosing in wild-type patients, which exposes them to an increased risk of thromboembolic events. Oake et al.[28] investigated the risk of adverse events in different INR ranges and demonstrated that although the risk of bleeding or thromboembolic events was lowest with an INR between two and three, an INR just above three was safer (less events) than an INR below 2. The results from the present study suggest that sensitive patients could be treated with smaller dose adjustments, thereby decreasing their bleeding risk, and that wild-type patients could be treated with larger dose adjustments to decrease the time below therapeutic INR range, thereby decreasing their risk of thromboembolic events. This knowledge is especially useful in the first months of therapy, as in the months thereafter the physician more

often uses the previous INRs and doses of a patient to determine the magnitude of dose adjustments.

In summary, the novel finding of the present study is that acenocoumarol users with the *CYP2C9* and *VKORC1* wild type have an increased risk of underanticoagulation in the first period of therapy. This suggests that pre-treatment genotyping could not only be useful in preventing overanticoagulation in the limited group of carriers of a *CYP2C9* and *VKORC1* polymorphism, but also to prevent underanticoagulation in the larger group of patients without a *CYP2C9* and *VKORC1* polymorphism. It has been suggested that pre-treatment genotyping could identify patients requiring a lower or higher coumarin dose, and thereby, reduce the risk of over anticoagulation or underanticoagulation in variant carriers and wild-type patients. Currently, the effectiveness and cost-effectiveness of a genotype-guided dosing regimen is being investigated in clinical trials[29-31]. If the genotype of a patient is known, this might help to prevent subtherapeutic or supratherapeutic INRs in the first months of therapy and thereby reduce the risk of adverse events. The trade-off between the health gained through this risk reduction and the extra costs of genotyping should be investigated in a cost-effectiveness analysis. As the costs of a genetic test are still decreasing, we believe that genotyping could be an attractive option in the future[32].

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SUPPLEMENT

Table S1. Characteristics of included acenocoumarol users in Pre-EU-PACT

Patients in study population (n=275)	VKORC1				CYP2C9			
	CC	CT	TT	missing:9	Wild-type	*2 carriers	*3 carriers	missing:10
	n=92	n=140	n=34		n=171	n=57	n=37	
Male	46 (50%)	82 (59%)	22 (65%)	p=0.25	97 (57%)	33 (58%)	20 (54%)	p=0.93
Mean age, years (median)	73 (75)	75 (77)	73 (75)	p=0.22	75 (76)	73 (75)	74 (74)	p=0.69
Mean height, cm (median)	172 (173)	173 (172)	173 (173)	p=0.82	172 (172)	174 (175)	172 (171)	p=0.55
Mean weight, kg (median)	82 (80)	81 (80)	77 (80)	p=0.59	80 (79)	82 (82)	81 (83)	p=0.50
Mean treatment duration, months (median)	27 (25)	29 (22)	41 (42)	**p=0.01**	29 (27)	29 (28)	33 (28)	p=0.79
Amiodaron users	3 (3%)	3 (2%)	1 (3%)	p=0.87	5 (3%)	1 (2%)	1 (3%)	p=0.89
Indication for coumarin therapy								
Atrial fibrillation	77 (84%)	119 (85%)	30 (88%)	p=0.82	145 (85%)	51 (90%)	29 (78%)	p=0.34
Venous thromboembolism	12 (13%)	18 (13%)	2 (6%)	p=0.50	19 (11%)	6 (11%)	7 (19%)	p=0.39
Other	3 (3%)	3 (2%)	2 (6%)	p=0.51	7 (4.1%)	0 (0%)	1 (3%)	p=0.29
Number of INR measurements								
0 – 1 month (n=275)	4.84	4.68	4.06	**p= 0.03**	4.78	4.47	4.35	p= 0.14
1 – 3 months (n=266)	5.39	5.01	4.30	**p= 0.002**	5.12	5.16	4.62	p= 0.33
3 – 6 months (n=233)	5.52	5.61	5.48	p= 0.94	5.79	5.02	5.4	**p= 0.04**
6 – 9 months (n=208)	5.31	5.37	5.18	p= 0.70	5.17	5.49	5.68	p= 0.21
9 – 12 months (n=190)	5.28	5.41	5.71	p= 0.36	5.25	5.41	6.16	p= 0.08
12 – 15 months (n=171)	5.07	4.74	5.04	p= 0.75	4.86	5.22	4.52	p= 0.55
15 – 18 months (n=162)	5.23	5.17	5.36	p= 1	5.23	5.00	5.55	p= 0.55

INR= International Normalised Ratio. Bold values indicate statistical significance (P < 0.05).

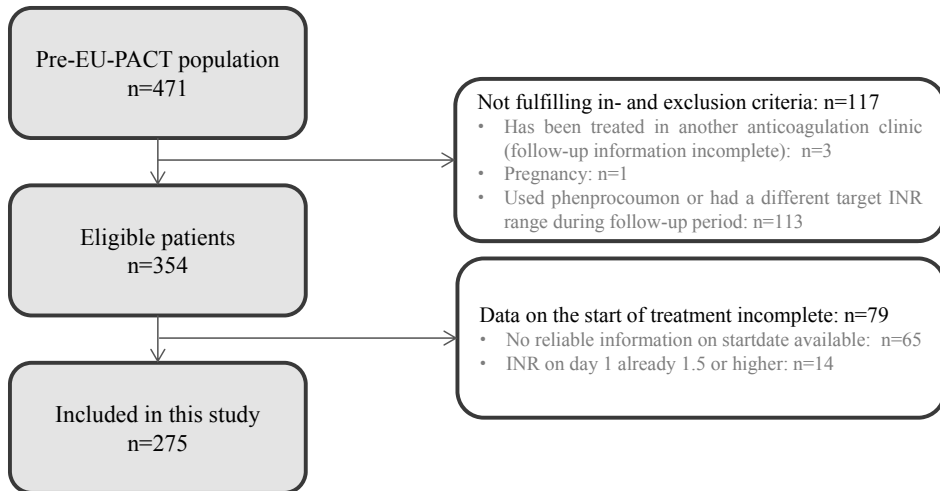**Table S2.** Characteristics of included acenocoumarol users in Schalekamp

Patients in study population (n=192)	VKORC1				CYP2C9			
	CC	CT	TT		Wild-type	*2 carriers	*3 carriers	
	n= 67	n= 89	n= 36		n= 123	n= 33	n= 36	
Male	35 (52%)	48 (54%)	20 (56%)	p= 0.95	65 (53%)	18 (55%)	20 (56%)	p= 0.95
Mean age, years (median)	68 (70)	66 (69)	63 (70)	p= 0.53	66 (70)	64 (67)	69 (79)	p= 0.61
Mean treatment duration, months (median)	5.1 (5.7)	5.0 (5.8)	4.4 (5.3)	p= 0.10	4.8 (5.7)	5.2 (5.7)	5.1 (5.9)	p= 0.26
Amiodaron users	0 (0%)	2 (2%)	0 (0%)	p= 0.31	1 (1%)	1 (3%)	0 (0%)	p= 0.43
Indication for coumarin therapy								
Atrial fibrillation	52 (78%)	62 (70%)	21 (58%)	p= 0.12	82 (67%)	27 (82%)	26 (72%)	p= 0.23
Venous thromboembolism	11 (16%)	17 (19%)	11 (31%)	p= 0.22	29 (24%)	4 (12%)	6 (17%)	p= 0.29
Other	3 (5%)	10 (11%)	4 (11%)	p= 0.30	12 (10%)	1 (3%)	4 (11%)	p= 0.42
Number of INR measurements								
0 – 1 month (n=188)	4.64	4.53	4.49	p= 0.76	4.50	4.63	4.69	p= 0.35
1 – 3 months (n=157)	4.97	4.86	4.12	**p= 0.05**	4.86	4.25	5.03	p= 0.13
3 – 6 months (n=130)	5.78	4.95	5.57	p= 0.08	5.56	5.04	5.08	p= 0.48

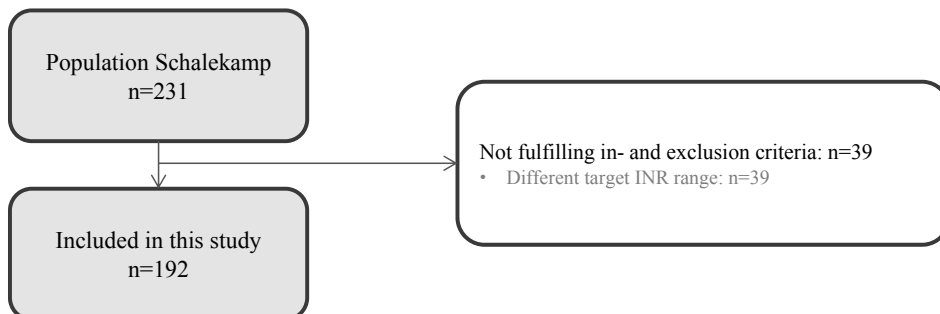INR= International Normalised Ratio. Bold values indicate statistical significance ($P < 0.05$).

Table S3. Characteristics of included acenocoumarol users in Rotterdam

Patients in study population (n=1119)	VKORC1				CYP2C9			
	CC	CT	TT		Wild-type	*2 carriers	*3 carriers	
	n= 340	n= 467	n= 141	missing: 171	n= 644	n= 222	n= 97	missing: 156
Male	118 (34%)	156 (33%)	45 (32%)	p= 0.83	226 (35%)	67 (30%)	32 (33%)	p= 0.41
Mean age, years (median)	75 (76)	78 (77)	76 (76)	p= 0.06	77 (77)	77 (77)	75 (75)	p= 0.20
Mean height, cm (median)	167 (165)	166 (165)	167 (166)	p= 0.42	166 (165)	166 (166)	168 (167)	p= 0.25
Mean weight, kg (median)	74 (74)	75 (74)	76 (76)	p=0.65	75 (74)	74 (7)	76 (76)	p=0.65
Mean treatment duration, months (median)	14.4 (3.6)	16.3 (3.5)	13.7 (3.1)	p= 0.49	15.5 (3.6)	13.1 (3.0)	16.1 (3.8)	p= 0.43
Amiodaron users	13 (4%)	8 (2%)	2 (1%)	p= 0.11	14 (2%)	5 (2%)	5 (5%)	p= 0.21
Indication for coumarin therapy								
Atrial fibrillation	114 (34%)	151 (32%)	46 (33%)	p= 0.94	218 (34%)	63 (28%)	33 (34%)	p= 0.31
Venous thromboembolism	58 (17%)	62 (13%)	27 (19%)	p= 0.15	88 (14%)	42 (19%)	20 (21%)	p= 0.06
Other	168 (49%)	254 (54%)	68 (48%)	p= 0.25	338 (53%)	117 (53%)	44 (45%)	p= 0.41
Number of INR measurements								
0 – 1 month (n=1021)	5.45	5.36	5.39	p= 0.65	5.37	5.42	5.49	p= 0.71
1 – 3 months (n=605)	4.88	4.67	4.88	p= 0.31	4.77	4.71	4.87	p= 0.87
3 – 6 months (n=423)	6.32	5.55	5.94	p= 0.003	5.83	5.96	5.98	p= 0.89
6 – 9 months (n=333)	5.60	5.60	5.49	p= 0.99	5.47	5.81	5.74	p= 0.31
9 – 12 months (n=299)	5.39	5.37	5.88	p= 0.71	5.36	5.71	5.48	p= 0.34
12 – 15 months (n=272)	5.45	5.09	5.23	p= 0.60	5.22	5.34	4.9	p= 0.55
15 – 18 months (n=252)	5.37	5.47	5.38	p= 0.82	5.43	5.70	4.80	p= 0.36

INR= International Normalised Ratio. Bold values indicate statistical significance (P < 0.05).

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┌─────────────────────────┐
│  Pre-EU-PACT population  │
│         n=471            │
└─────────────────────────┘
             │          ┌──────────────────────────────────────────────────────┐
             │          │ Not fulfilling in- and exclusion criteria: n=117     │
             ├─────────▶│ •  Has been treated in another anticoagulation clinic│
             │          │    (follow-up information incomplete):  n=3          │
             │          │ •  Pregnancy: n=1                                    │
             │          │ •  Used phenprocoumon or had a different target INR  │
             │          │    range during follow-up period: n=113             │
             ▼          └──────────────────────────────────────────────────────┘
┌─────────────────────────┐
│    Eligible patients     │
│         n=354            │
└─────────────────────────┘
             │          ┌──────────────────────────────────────────────────────┐
             │          │ Data on the start of treatment incomplete: n=79      │
             ├─────────▶│ •  No reliable information on startdate available: n=65│
             │          │ •  INR on day 1 already 1.5 or higher: n=14          │
             ▼          └──────────────────────────────────────────────────────┘
┌─────────────────────────┐
│  Included in this study  │
│         n=275            │
└─────────────────────────┘
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Figure S1a. Selection of patients from Pre-EU-PACT

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┌─────────────────────────┐
│  Population Schalekamp   │
│         n=231            │
└─────────────────────────┘
             │          ┌──────────────────────────────────────────────────────┐
             ├─────────▶│ Not fulfilling in- and exclusion criteria: n=39      │
             │          │ •  Different target INR range: n=39                  │
             ▼          └──────────────────────────────────────────────────────┘
┌─────────────────────────┐
│  Included in this study  │
│         n=192            │
└─────────────────────────┘
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Figure S1b. Selection of patients from the study of Schalekamp

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┌─────────────────────────┐
│    ERGO1 population      │
│         n=2065           │
└─────────────────────────┘
             │          ┌──────────────────────────────────────────────────────┐
             ├─────────▶│ Not fulfilling in- and exclusion criteria: n=946     │
             │          │ •  Different target INR range: n=946                 │
             ▼          └──────────────────────────────────────────────────────┘
┌─────────────────────────┐
│  Included in this study  │
│         n=1119           │
└─────────────────────────┘
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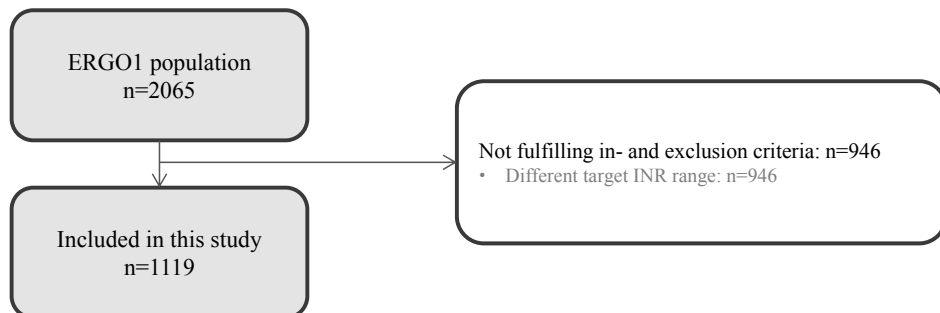
Figure S1c. Selection of patients from the Rotterdam study
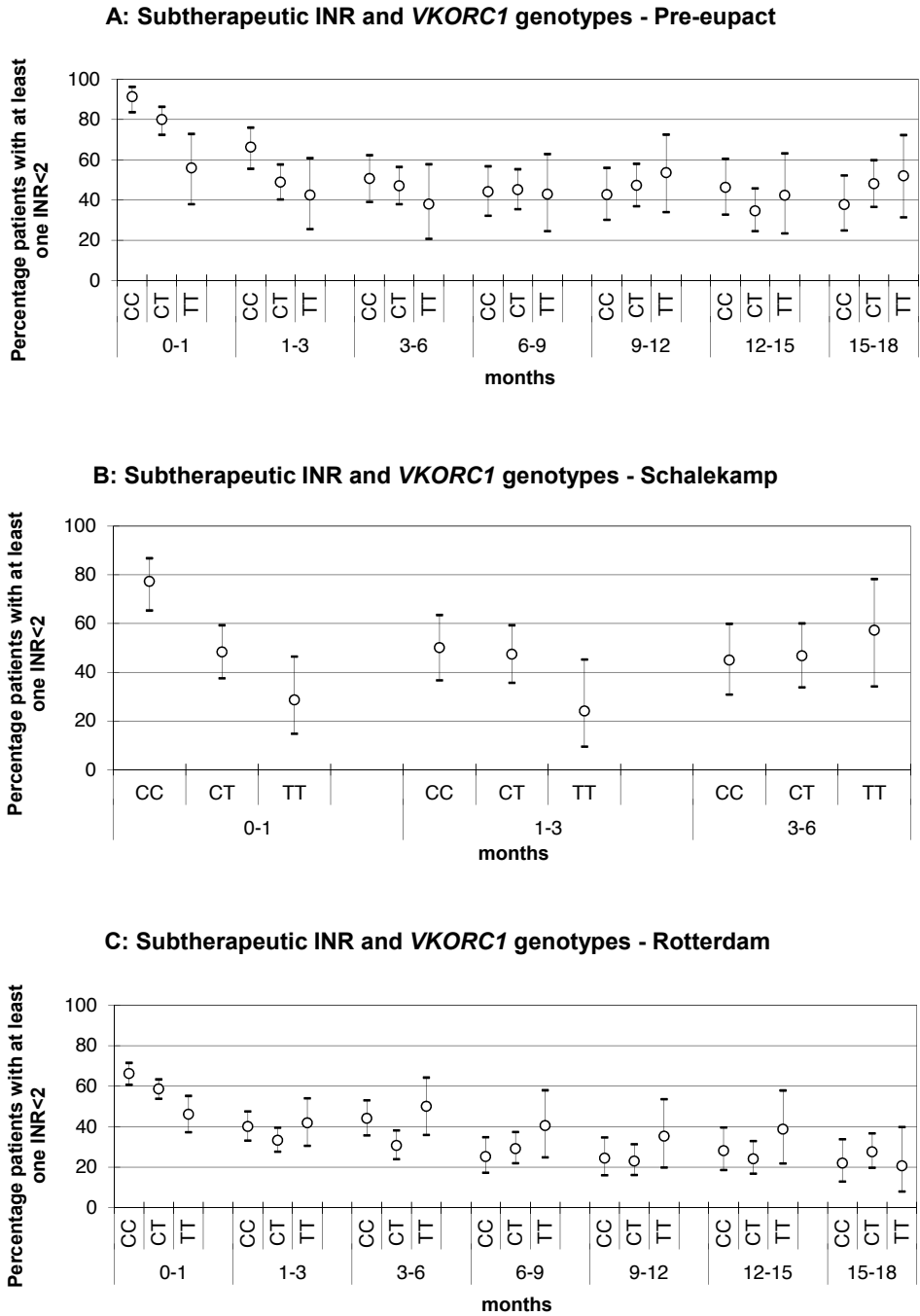
A: Subtherapeutic INR and *VKORC1* genotypes - Pre-eupact

B: Subtherapeutic INR and *VKORC1* genotypes - Schalekamp
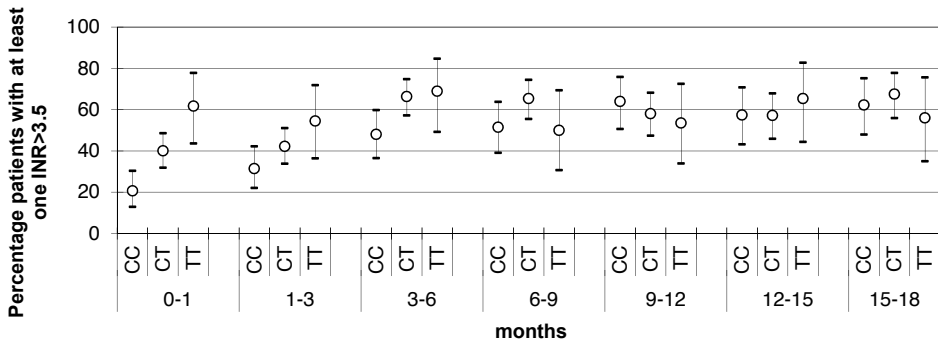

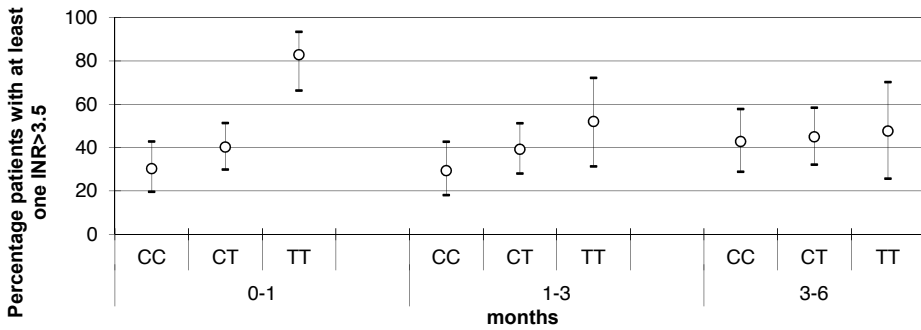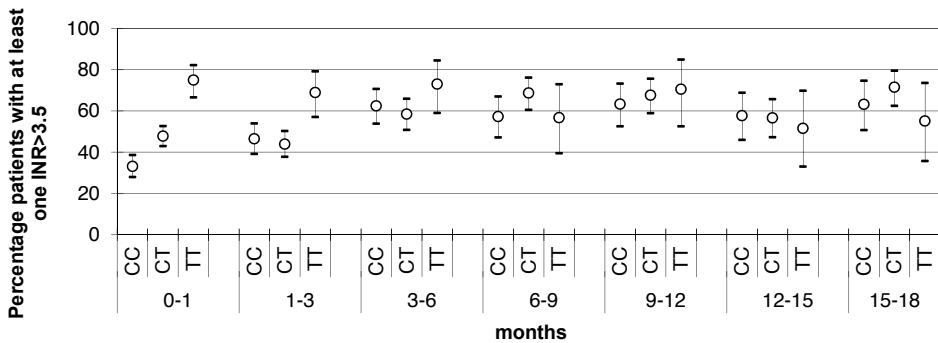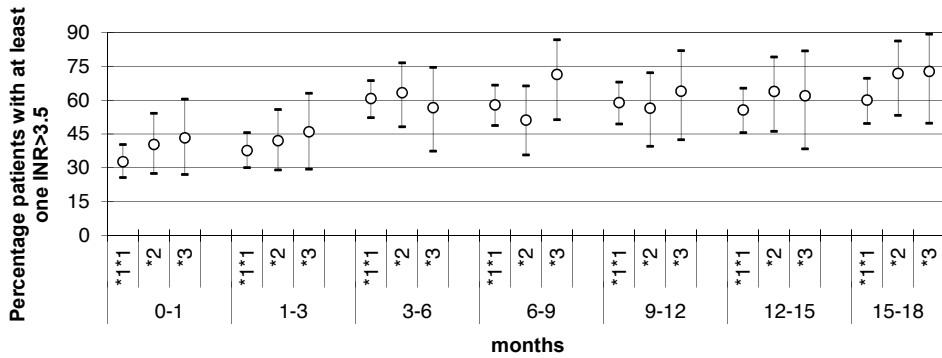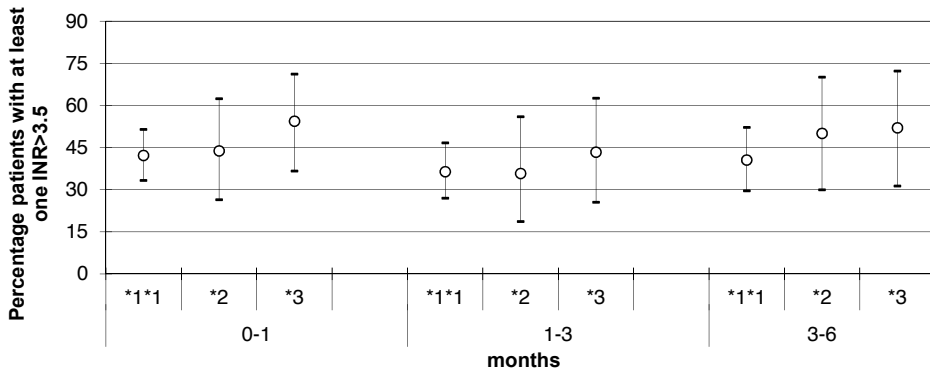**C: Subtherapeutic INR and *VKORC1* genotypes - Rotterdam**

Figure S2. Percentage of patients (and 95% confidence intervals) with at least one INR<2 in the different time periods after coumarin initiation – *VKORC1* genotypes. A: Pre-EU-PACT, B: Schalekamp, C: Rotterdam.
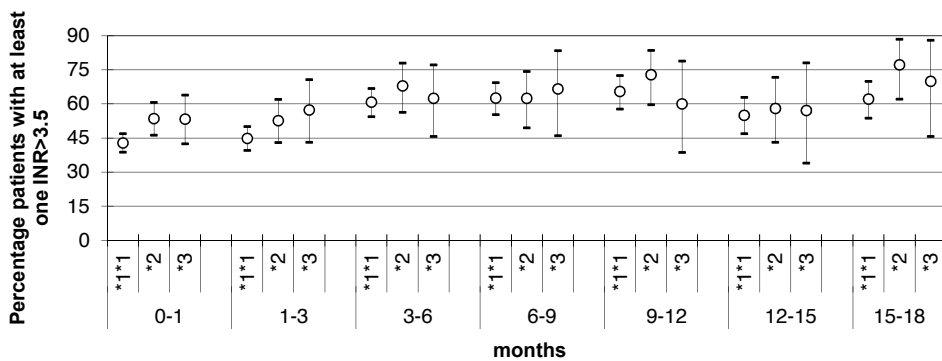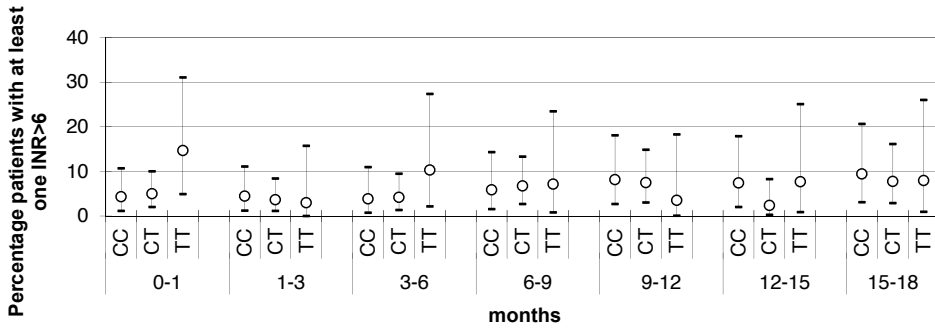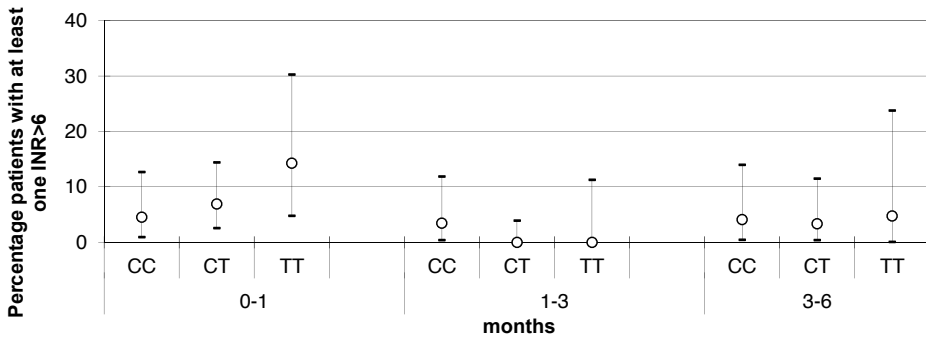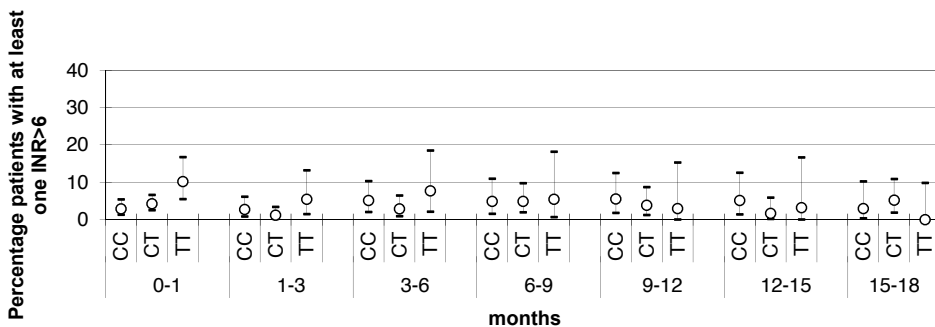
A: Subtherapeutic INR and *CYP2C9* genotypes - Pre-eupact
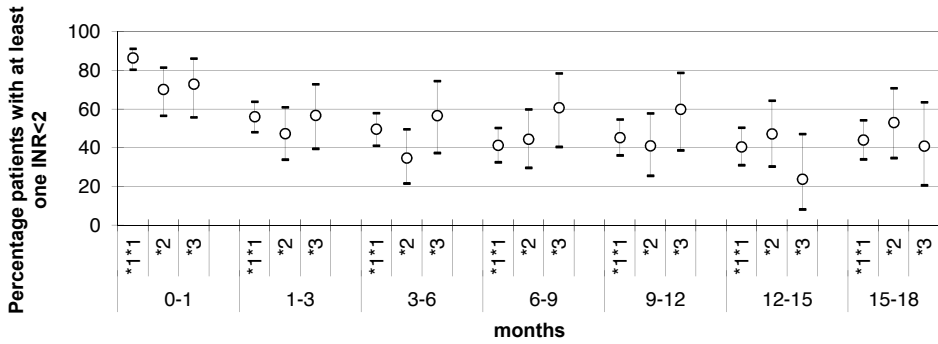
B: Subtherapeutic INR and *CYP2C9* genotypes - Schalekamp
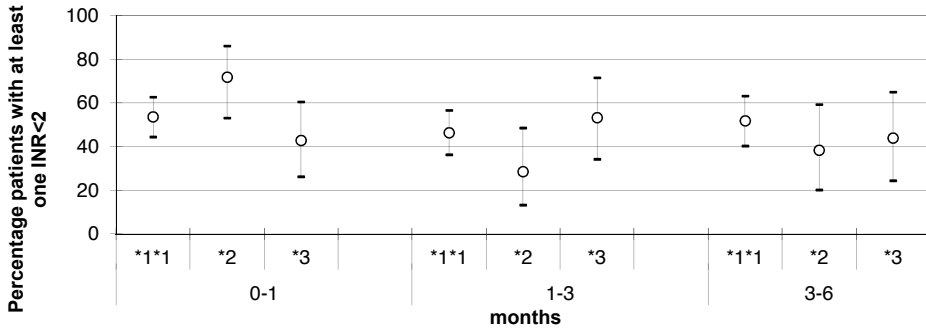
C: Subtherapeutic INR and *CYP2C9* genotypes - Rotterdam
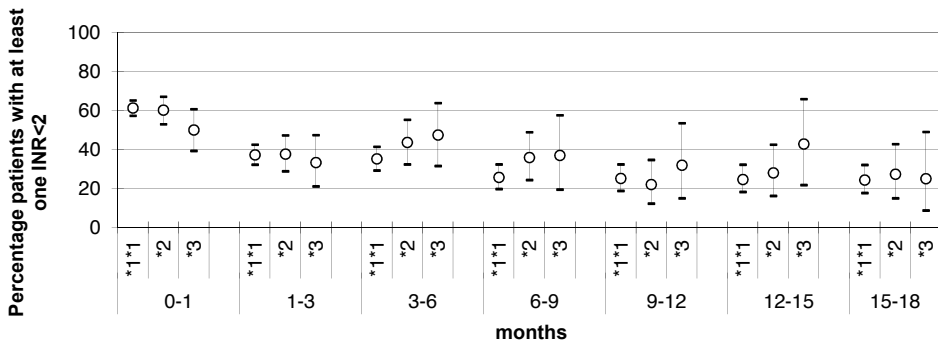
Figure S3. Percentage of patients (and 95% confidence intervals) with at least one INR<2 in the different time periods after coumarin initiation – *CYP2C9* genotypes. A: Pre-EU-PACT, B: Schalekamp, C: Rotterdam.

**A: Supratherapeutic INR and *VKORC1* genotypes - Pre-eupact**

B: Supratherapeutic INR and *VKORC1* genotypes - Schalekamp

C: Supratherapeutic INR and *VKORC1* genotypes - Rotterdam

Figure S4. Percentage of patients (and 95% confidence intervals) with at least one INR>3.5 in the different time periods after coumarin initiation – *VKORC1* genotypes. A: Pre-EU-PACT, B: Schalekamp, C: Rotterdam

A: Supratherapeutic INR and *CYP2C9* genotypes - Pre-eupact

B: Supratherapeutic INR and *CYP2C9* genotypes - Schalekamp

C: Supratherapeutic INR and *CYP2C9* genotypes - Rotterdam

Figure S5. Percentage of patients (and 95% confidence intervals) with at least one INR>3.5 in the different time periods after coumarin initiation – *CYP2C9* genotypes. A: Pre-EU-PACT, B: Schalekamp, C: Rotterdam

A: Severe overanticoagulation and *VKORC1* genotypes - Pre-eupact

B: Severe overanticoagulation and *VKORC1* genotypes - Schalekamp

C: Severe overanticoagulation and *VKORC1* genotypes - Rotterdam

Figure S6. Percentage of patients (and 95% confidence intervals) with at least one INR>6 in the different time periods after coumarin initiation – *VKORC1* genotypes. A: Pre-EU-PACT, B: Schalekamp, C: Rotterdam

A: Severe overanticoagulation and *CYP2C9* genotypes - Pre-eupact
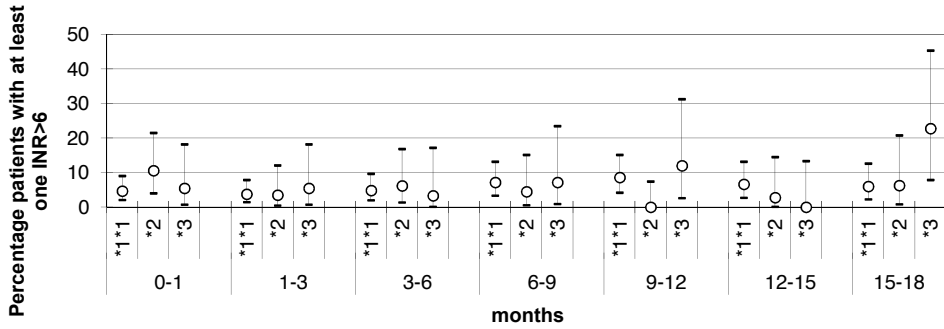
B: Severe overanticoagulation and *CYP2C9* genotypes - Schalekamp
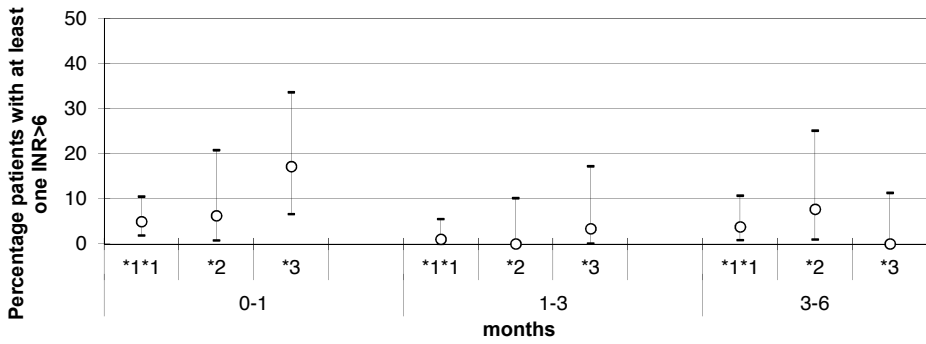
C: Severe overanticoagulation and *CYP2C9* genotypes - Rotterdam
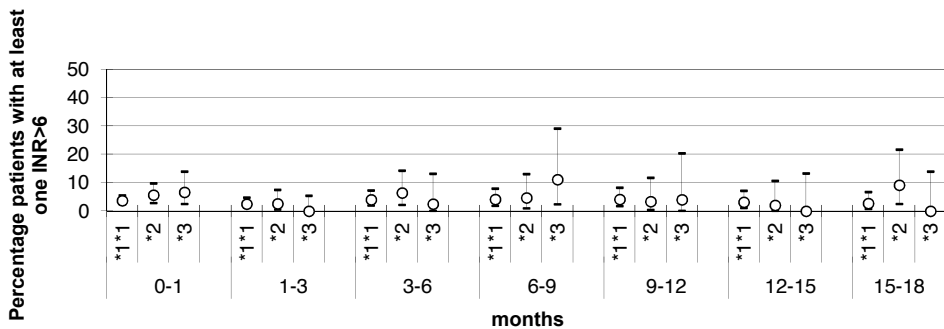
Figure S7. Percentage of patients (and 95% confidence intervals) with at least one INR>6 in the different time periods after coumarin initiation – *CYP2C9* genotypes. A: Pre-EU-PACT, B: Schalekamp, C: Rotterdam

LONG-TERM ANTICOAGULANT EFFECTS OF *CYP2C9* AND *VKORC1* GENOTYPES IN PHENPROCOUMON USERS

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Anticoagulant treatment with phenprocoumon is challenging because of the narrow therapeutic range and the wide inter- and intra-patient variability in dose response. Frequent monitoring of the international normalised ratio (INR) is therefore required. Polymorphisms in two genes, *CYP2C9* and *VKORC1*, explain approximately one-third of the variation in dose requirements [1-3]. *CYP2C9* encodes the main metabolizing enzyme of coumarin anticoagulants, the cytochrome P450 2C9 enzyme (CYP2C9), while *VKORC1* encodes the pharmacodynamics target enzyme for coumarin anticoagulants, vitamin K epoxide reductase multiprotein complex 1 (VKORC1).

Earlier this year, we found that in the first month of acenocoumarol therapy, the risk of underdosing is highest in patients with a *VKORC1* wild type [4]. This increased risk of a subtherapeutic INR was also seen in months 2 and 3, but not after the third month of coumarin treatment. In addition, the risk of overdosing was highest in patients with a *VKORC1* TT genotype in the first 6 months. The effect of *CYP2C9* genotype on under- or overdosing of acenocoumarol was smaller than the effect of *VKORC1* and this effect was only found in the first month of therapy and not after the initiation period [4]. This has not been investigated for phenprocoumon yet. The aim of this study was therefore to examine the association of *CYP2C9* and *VKORC1* polymorphisms with the risk of over- and under-anticoagulation after the initiation period of phenprocoumon.

To investigate this, we looked at data from two different studies, the pre-EU-PACT study [5] and the study by Schalekamp et al. [6]. The study protocols of both studies were approved by a Medical Ethics Committee (Leiden University Medical Center, Leiden, for the pre-EU-PACT study, and Utrecht Medical Centre, Utrecht, for the study by Schalekamp) and patients provided informed consent before study inclusion. All procedures were conducted in accordance with the Helsinki Declaration. More details about the design and data collection in both studies can be found elsewhere [4].

We examined the occurrence of at least one INR < 2,> 3.5 or> 6.0 in several time periods up to 1.5 years after treatment initiation and tested for differences among the genotypes with chi-square analysis. The time periods we used were: 0–1 month (days 1–30), 1–3 months (days 31–90), 3–6 months (days 91–180), 6–9 months (days 181–270), 9–12 months (days 271–360), 12–15 months (days 361–450) and 15–18 months (days 451–540) after treatment initiation. We also looked at the time within, below and above the therapeutic range, because this method is more robust when the frequency of INR measurements differs between patients. All analyses were performed using SPSS 18.0 (SPSS Inc., Chicago, IL, USA).

In total, 794 phenprocoumon users from the two studies [5,6] were eligible for analyses in this study. Patient characteristics and genotypes of all 794 patients are shown in the Supplement Table S1. Data on height and weight were only available in the Pre-EU-PACT study (n = 486). The most frequent indication for phenprocoumon treatment was atrial fibrillation. The average number of INR measurements per time period ranged from 3.4 to 5.5. Only data

of patients using phenprocoumon during the entire time period were included in the analysis of that period. The maximum follow-up in the Schalekamp study was 6 months (n = 308).

Significant differences in out-of-range INR values between the genotypes were only found during the first month of phenprocoumon therapy. In the first month, 89% of the patients with a *VKORC1* wild type had at least one subtherapeutic INR. This frequency was significantly lower among patients with CT (76%, P < 0.001) and TT (50%, P < 0.001). Supratherapeutic INR values occurred in 33% of the *VKORC1* wild-type patients, vs. 48% (P < 0.001) and 66% (P < 0.001) in patients with a CT or TT genotype, respectively. Of the wild-type patients, 3% had at least one INR > 6. This percentage was increased in patients with a TT genotype (17%, P < 0.001), but there was no statistically significant difference for patients with a CT genotype (6%, P = 0.12).

Occurrences of subtherapeutic INR values or INR values > 6 were not significantly different among the *CYP2C9* genotypes. However, INR values > 3.5 occurred more often in carriers of a *CYP2C9**3 allele (62%, P < 0.001) or a *CYP2C9**2 allele (52%, P = 0.01) than in wild-type patients (40%). For both *VKORC1* and *CYP2C9* genotypes, no significant differences in out-of-range INRs were found after the first month. The risk of out-of-range INRs for the different periods and genotypes is shown in the Supplement (Figures S1–S4).

Similar results were obtained in the analyses of time within, below and above therapeutic INR range (Figure 1). In the first month, time below therapeutic INR range was longest in *VKORC1* and *CYP2C9* wild-type patients (up to 33%) and time above therapeutic INR range was longest in *VKORC1*–TT and *CYP2C9**3 carriers (up to 37%). The risk of having at least one INR < 2 did not vary significantly among the *CYP2C9* genotypes, but the time spent below therapeutic INR range was significantly shorter in *2 carriers (19%) and *3 carriers (14%) than in wild-type patients (26%, P < 0.001). No significant differences were found after month 1 of the treatment.

Our study demonstrated that in the first month of phenprocoumon therapy, the risk of underdosing is highest in patients with *VKORC1* and *CYP2C9* wild types. In addition, the risk of overdosing was highest in patients with a *VKORC1* TT genotype or carriers of a *CYP2C9* variant allele. These results correspond with the results we have seen for acenocoumarol users, as described in a previous article [4]. However, the results beyond the first month of treatment are not similar. Specifically, while there were no differences in the risk of out-of-range INRs between the different genotypes after the first month of phenprocoumon therapy, there were differences in risk between the *VKORC1* genotypes up to the sixth month of acenocoumarol treatment.

A limitation of this study is the fact that the Pre-EUPACT study contained retrospective data [5]. The data of Schalekamp et al. [6], however, were collected prospectively. Data for a specific time period were only used in the analysis if the patient used phenprocoumon for this entire period. Because very unstable

A: *VKORC1* genotypes
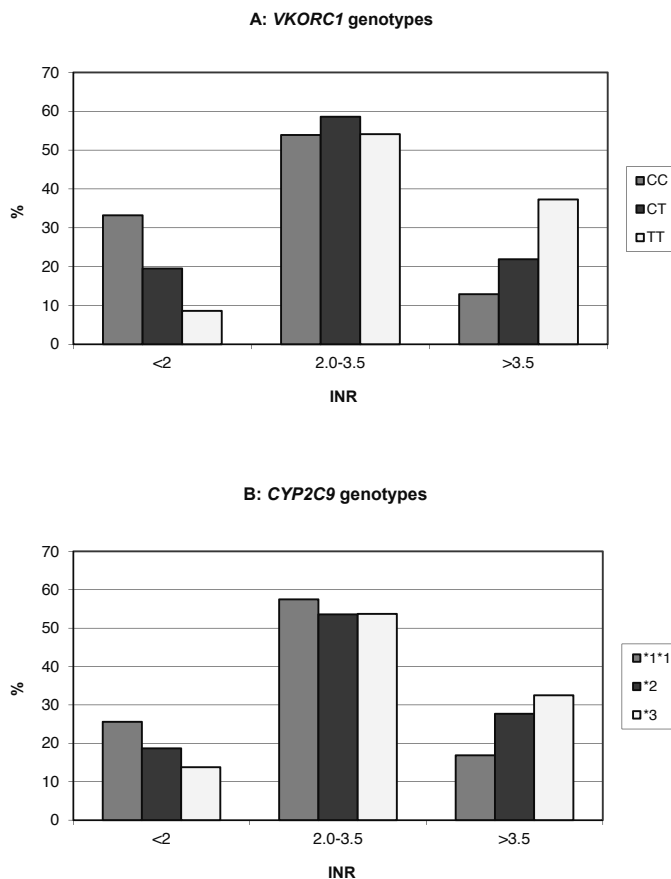
B: *CYP2C9* genotypes

Figure 1. Percentage time in different INR ranges during the first month of phenprocoumon use. A: *VKORC1* genotypes, **B**: *CYP2C9* genotypes.

patients are expected to stop the therapy early, this patient group might be under-represented in our study.

Information about the patient's genotype can be used to predict the right dose of phenprocoumon [5]. Carriers of a *VKORC1* or *CYP2C9* variant allele require a lower dose and have an increased risk of supratherapeutic INR values. If these patients are genotyped before treatment initiation, they could be treated with a lower dose, thereby decreasing the risk of over-anticoagulation. In both this study and our previous study on acenocoumarol, we also found an increased risk of a subtherapeutic INR in *VKORC1* and *CYP2C9* wild-type patients during the first month. Information about the patient's genotype could therefore also be used to identify patients who need a higher dose to decrease the risk of complications from underdosing. In this way, genetic information could be used to improve the safety and efficacy of anticoagulation treatment in both wild-type patients and variant carriers. The relevance

of pharmacogenetic information for phenprocoumon users, however, seems to be limited to the first month of treatment.

Phenprocoumon has a longer elimination half-life than acenocoumarol (110–130 h vs. 6–8 h) [3,7]. Treatment with phenprocoumon is therefore somewhat more stable and patients on phenprocoumon spend more time within the therapeutic INR range than patients on acenocoumarol [8]. This might be a reason why only acenocoumarol users, and not phenprocoumon users, show differences between the genotypes in the risk of out-of-range INRs after the first month of treatment.

The results of this study suggest that pharmacogenetic information might help to prevent subtherapeutic or supratherapeutic INRs in the first month of phenprocoumon therapy and thereby reduce the risk of adverse events. The value of this information after the first month of phenprocoumon treatment appears to be limited. Currently, clinical trials are underway to investigate the effectiveness and cost-effectiveness of a genotype-guided dosing regimen vs. a standard dosing regimen [9,10].

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SUPPLEMENT

Table S1. Characteristics of included phenprocoumon users

Patients in study population (n=794)	VKORC1				CYP2C9			
	CC	CT	TT		Wild-type	*2 carriers	*3 carriers	
	n= 280	n= 341	n= 126	missing: 47	n= 497	n= 158	n= 94	missing: 45
Male	156 (56%)	190 (56%)	76 (60%)	p= 0.64	276 (56%)	96 (61%)	50 (53%)	p= 0.41
Mean age, years (median)	69 (71)	68 (70)	68 (71)	p= 0.92	68 (71)	68 (70)	68 (72)	p= 0.95
Mean height, cm (median)	173 (172)	172 (172)	173 (172)	p= 0.69	172 (172)	174 (176)	172 (171)	p= 0.06
Mean weight, kg (median)	82 (80)	82 (80)	79 (77)	p= 0.39	81 (80)	81 (80)	80 (77)	p= 0.82
Mean treatment duration, months (median)	29.7 (11.5)	30.6 (13.1)	30.8 (9.5)	p= 0.57	29.9 (13.1)	31.2 (9.2)	30.4 (11.1)	p= 0.87
Indication for coumarin therapy								
Atrial fibrillation	211 (75%)	258 (76%)	90 (71%)	p= 0.63	372 (75%)	120 (76%)	67 (71%)	p= 0.70
Venous thromboembolism	59 (21%)	74 (22%)	30 (24%)	p= 0.82	111 (22%)	34 (22%)	20 (21%)	p= 0.96
Other	10 (4%)	9 (3%)	6 (5%)	p= 0.51	14 (3%)	4 (3%)	7 (7%)	p= 0.06
Number of INR measurements								
0 – 1 month (n=790)	5.54	4.58	4.70	p= 0.40	4.59	4.54	4.66	p= 0.64
1 – 3 months (n=734)	4.91	4.83	5.12	p= 0.19	4.87	5.10	4.82	p= 0.36
3 – 6 months (n=663)	4.87	4.93	4.96	p= 0.89	4.88	5.13	4.81	p= 0.41
6 – 9 months (n=401)	4.34	4.23	4.28	p= 0.98	4.20	4.62	4.19	p= 0.15
9 – 12 months (n=378)	4.14	4.02	4.11	p= 0.76	4.20	4.05	3.39	**p= 0.02**
12 – 15 months (n=361)	4.00	4.00	3.89	p= 0.71	4.11	3.77	3.65	p= 0.16
15 – 18 months (n=343)	3.86	3.76	3.71	p= 0.82	3.86	3.62	3.73	p= 0.55

INR= International Normalised Ratio. Bold values indicate statistical significance (P < 0.05).
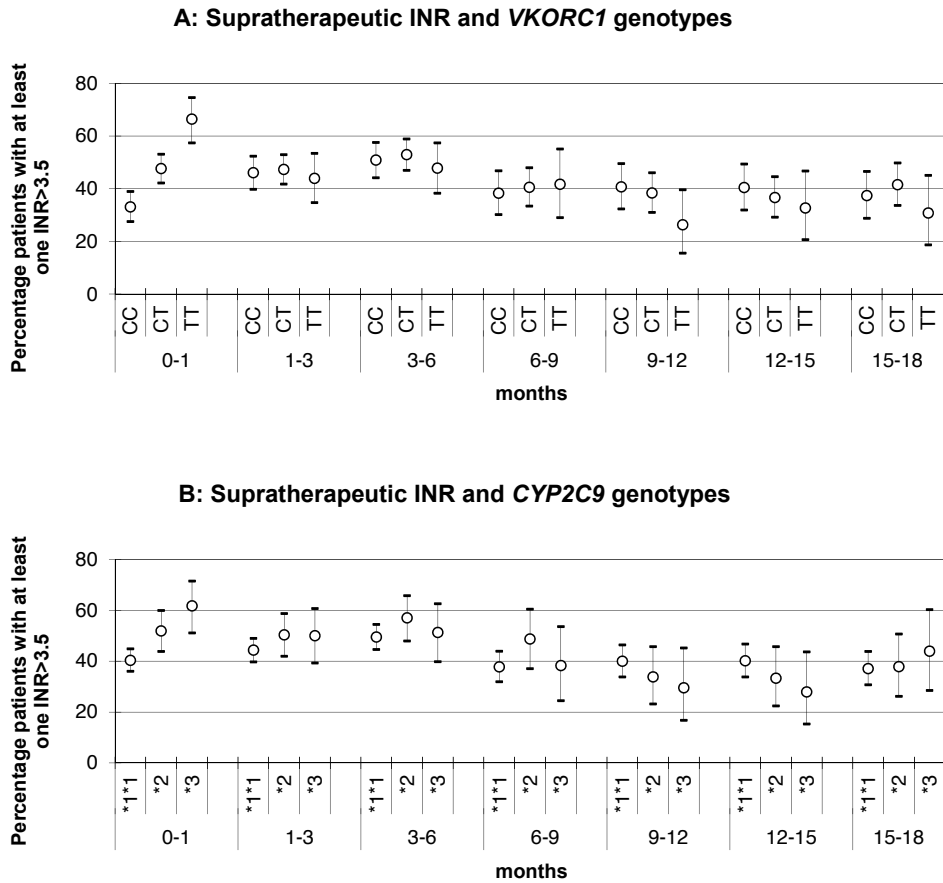
4

A: Subtherapeutic INR and *VKORC1* genotypes
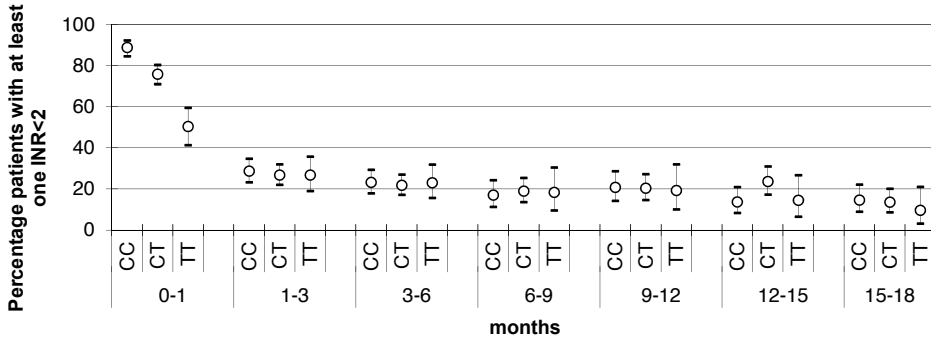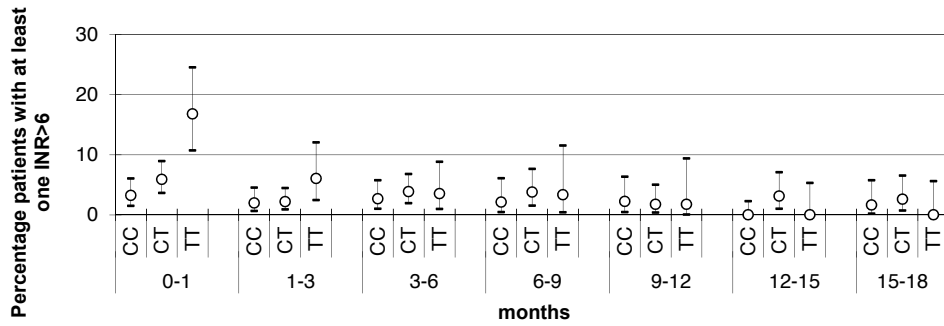

B: Subtherapeutic INR and *CYP2C9* genotypes
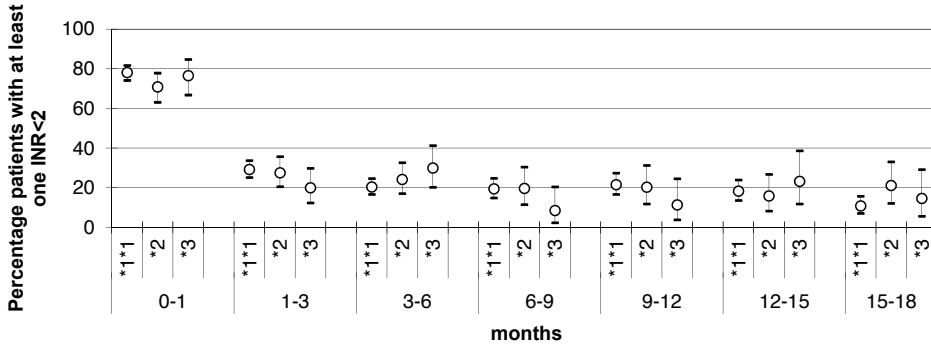
Figure S1. Percentage of patients (and 95% confidence intervals) with at least one INR<2 in the different time periods after coumarin initiation. A: *VKORC1* genotypes B: *CYP2C9* genotypes
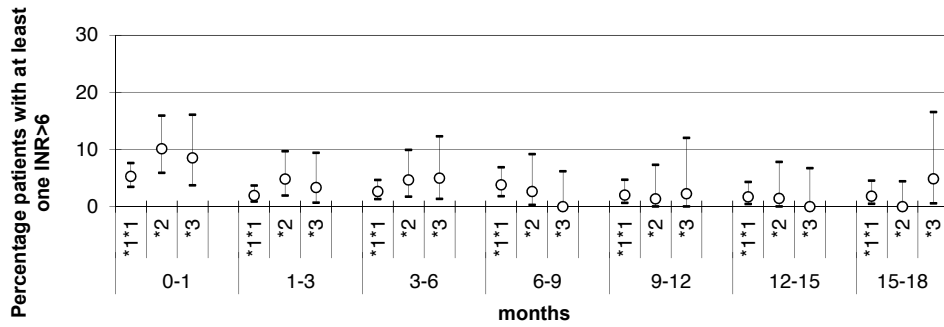
A: Supratherapeutic INR and *VKORC1* genotypes

B: Supratherapeutic INR and *CYP2C9* genotypes

Figure S2. Percentage of patients (and 95% confidence intervals) with at least one INR>3.5 in the different time periods after coumarin initiation. A: *VKORC1* genotypes B: *CYP2C9* genotypes

A: Severe overanticoagulation and *VKORC1* genotypes

**B: Severe overanticoagulation and *CYP2C9* genotypes**

Figure S3. Percentage of patients (and 95% confidence intervals) with at least one INR>6 in the different time periods after coumarin initiation. A: *VKORC1* genotypes B: *CYP2C9* genotypes
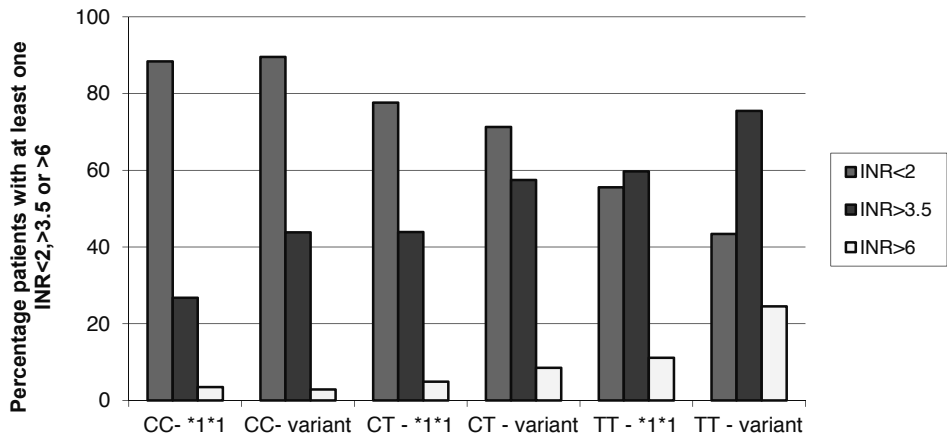
Figure S4. Risk of under- or overanticoagulation during the first month of coumarin treatment and combined *VKORC1/ CYP2C9* genotypes
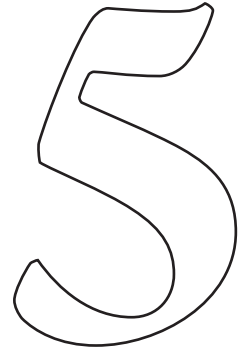
THE EFFECT OF OMEPRAZOLE AND ESOMEPRAZOLE ON THE MAINTENANCE DOSE OF PHENPROCOUMON

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The response to vitamin K antagonists (VKAs) is determined by many different factors like age, weight, height, vitamin K intake and genetic polymorphisms [1]. The proton pump inhibitors (PPIs) omeprazole and esomeprazole may enhance the effect of VKAs by inhibition of the hepatic metabolism of coumarin anticoagulants [2]. Some isolated cases have been reported of clinically significant elevated INRs in patients concomitantly using omeprazole and phenprocoumon, a VKA frequently used in Europe [3]. Practical experience suggests an interaction between omeprazole or esomeprazole and phenprocoumon, but scientific evidence is still lacking.

Van Schie et al. developed a dosing algorithm including age, gender, height, weight, CYP2C9 and VKORC1 genotypes and amiodarone use and a dosing algorithm without the genotypes to predict the phenprocoumon maintenance dose [4]. Given the possibility that omeprazole use affects the stable phenprocoumon maintenance dose, we examined whether information about its use would improve the predictive value of a dosing algorithm.

Data from the pre-EU-PACT study were used to study the effect of omeprazole and esomeprazole on the stable phenprocoumon maintenance dose [4]. More details about this study can be found elsewhere [4]. The main outcome measure of the present study was the mean stable phenprocoumon maintenance dose in mg/day in the first stable period after initiation of phenprocoumon therapy. Only patients who reached a stable dose within 1 year were included in the analyses. Multiple linear regression analysis was used to develop a genotype-guided

algorithm and a non-genotype-guided algorithm to estimate the square root of the weekly phenprocoumon maintenance dose. We included the same predictive variables used by van Schie et al. [4], but added an extra variable for omeprazole or esomeprazole use.

A stable maintenance dose was reached within 1 year by 597 patients. Of these, 46 patients used omeprazole and 18 patients used esomeprazole. On average, non-users required 2.27 mg (SD 0.90) phenprocoumon per day, significantly higher than the average dose seen in both omeprazole users (1.78 mg/day, SD 0.73, 95% CI of the difference 0.22, 0.75) and esomeprazole users (1.88 mg/day, SD 0.52, 95% CI of the difference 0.12, 0.66)). Since the phenprocoumon dose was not significantly different

between omeprazole and esomeprazole users (95% CI of the difference -0.47, 0.28), we combined them into one group for inclusion in the algorithm. Five hundred and eighty-seven phenprocoumon users were included in the analysis of the non-genotype-guided algorithm and 559 for the genotype-guided algorithm. Omeprazole/esomeprazole use significantly influenced the phenprocoumon maintenance dose in the genotype-guided algorithm ($P = 0.002$) and the non-genotype-guided algorithm ($P = 0.001$) (Table 1).

The genotype-guided algorithm was as follows:

SQRT (maintenance dose (mg/week)) = 2.870–0.254 (if CYP2C9*1/*2) – 0.356 (if CYP2C9*1/*3) – 0.431 (if CYP2C9*2/*2) – 0.708 (if CYP2C9*2/*3) – 0.693 (if CYP2C9*3/*3) – 0.594 (if VKORC1 CT) – 1.371 (if VKORC1 TT) – 0.015 x Age (years) + 0.034 (if female)

Table 1. Algorithms to predict stable phenprocoumon maintenance dose

	Genotype-guided algorithm	P value	Non-genotype-guided algorithm	P value	Univariate r^2
Intercept	2.870		1.659		
CYP2C9 genotype		<0.001		-	5.1
*1/*1	0		-		
*1/*2	-0.254		-		
*1/*3	-0.356		-		
*2/*2	-0.431		-		
*2/*3	-0.708		-		
*3/*3	-0.693		-		
VKORC1 genotype		<0.001		-	34.3
CC	0		-		
CT	-0.594		-		
TT	-1.371		-		
Age (years)	-0.015	<0.001	-0.010	0.001	8.3
Gender, if female	0.034	0.579	0.109	0.174	2.3
Height (cm)	0.011	0.001	0.011	0.020	7.2
Weight (kg)	0.009	<0.001	0.013	<0.001	13.1
Amiodarone use, if yes	-0.315	0.003	-0.304	0.032	0.4
Omeprazole/esomeprazole use, if yes	-0.234	0.002	-0.323	0.001	2.5
Unadjusted r^2 of the algorithm	56.7%		18.9%		

NB, Dependent variable is the square root of the stable maintenance dose of phenprocoumon.

+ 0.009 x Weight (kg) + 0.011 x Height (cm) – 0.315 (if amiodarone use) – 0.234 (if omeprazole/esomeprazole use).

With this genotype-guided algorithm, 56.7% of dose variation could be explained, 0.8% more than in the study of van Schie *et al.* [4].With our non-genotype-guided algorithm, the predictive value was 18.9%, 1.6% more than the algorithm of van Schie *et al.* [4].

The information obtained in this study could help physicians determine the right phenprocoumon dose for patients. If a patient is already using omeprazole or esomeprazole when phenprocoumon treatment is started, the dosing algorithm can be used to predict the required dose. If a patient starts using omeprazole or esomeprazole during phenprocoumon treatment the dose of phenprocoumon should be lowered. This could help prevent overanticoagulation and thereby reduce the risk of bleeding events when phenprocoumon and omeprazole or esomeprazole are used simultaneously.

In this study we observed a lower phenprocoumon dose requirement in omeprazole and esomeprazole users and

developed a dosing algorithm using this information. We only demonstrated the effect of omeprazole and esomeprazole.

An interaction between phenprocoumon and other PPIs should be investigated in future research.

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BELIEFS ABOUT MEDICINES IN DUTCH ACENOCOUMAROL AND PHENPROCOUMON USERS

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ABSTRACT

Introduction: Adherence to the mostly complex regimen of coumarin derivatives is vital in order to keep patients in the adequate INR range. Patients' beliefs about medicines are associated with the level of therapy adherence. Our aim was to assess the beliefs about coumarin anticoagulants. Secondly we compared the beliefs about coumarin anticoagulants with the beliefs about other cardiovascular drugs.

Methods: The Beliefs about Medicines Questionnaire (BMQ) was used to assess medication beliefs. The BMQ was completed by users of coumarin anticoagulants indicated for venous thromboembolism or atrial fibrillation. A necessity and a concerns score was calculated for all patients. The analyses were repeated for users of antihypertensive drugs or statins (not using coumarin anticoagulants).

Results: 320 patients were included in the analysis on the beliefs about coumarin anticoagulants. The mean necessity score was 15.3, the concerns score 12.3 and the necessity-concerns differential 3.0. Patients with venous thromboembolism (n=71) had higher necessity scores than patients with atrial fibrillation (n=249) (16.8 vs. 14.9, p<0.001). The mean necessity score in 493 users of other cardiovascular drugs was 16.1, the concerns score 13.5 and the necessity-concerns differential 2.6. The necessity score was higher in chronic cardiovascular drug users (n=192) than in new users (n=301) (17.9 vs. 14.9, p<0.001).

Conclusions: Coumarin users score higher on the necessity scale than on the concerns scale, which is also the case in users of other cardiovascular drugs. Patients with atrial fibrillation have a less positive attitude towards these drugs than patients with venous thromboembolism, and could therefore benefit more from specific attention.

INTRODUCTION

Patient beliefs about medicines are an important factor in the adherence to the therapy. Patients can have concerns about, for example, the side effects of the drug or they can believe that the drug is not really necessary for their health. Several studies have shown that higher concerns about medication as well as lower necessity beliefs are associated with higher non-adherence [1-5]. Non-adherence is a significant challenge to clinical practice and for some patients extra education might be useful to increase adherence. Knowledge about patient beliefs might help to identify patients who would benefit

from additional counselling. The Beliefs about Medicines Questionnaire (BMQ) was developed to simplify the wide range of beliefs that patients may have about their medication [6].

The BMQ has not yet been applied in studies focusing on anticoagulant therapy with coumarin derivatives. The coumarin derivatives acenocoumarol, phenprocoumon and warfarin are frequently used for the treatment and prevention of thromboembolic events in patients with, for example, atrial fibrillation or venous thromboembolism [7]. These drugs have a narrow therapeutic range

and show large inter- and intra-individual variation in dose requirements. Frequent monitoring of the level of anticoagulation and adjusting the dose is required. This makes the treatment with coumarin anticoagulants more burdensome than most other cardiovascular drugs. On the other hand, it is possible that the therapy adherence is higher in these drugs than in other cardiovascular drugs, because of the frequent checks. Analysing the beliefs of patients using coumarin derivatives can provide insight into their attitude towards their treatment. The aim of this study was therefore: to assess the beliefs about acenocoumarol and phenprocoumon in patients initiating therapy with these drugs for atrial fibrillation or venous thromboembolism. A secondary aim was to compare the beliefs about coumarin derivatives with the beliefs about other cardiovascular drugs (antihypertensive drugs or statins).

MATERIALS AND METHODS

Participants

The European pharmacogenetics of oral anticoagulation (EU-PACT) trial aims to assess the effectiveness of pharmacogenetic-guided dosing of coumarin derivatives and includes patients starting acenocoumarol, phenprocoumon or warfarin therapy for either atrial fibrillation (AF) or venous thromboembolism (VTE) [8]. Patients were recruited at four different anticoagulation clinics in The Netherlands. More details about the EU-PACT trial can be found elsewhere [8]. After approximately one week of therapy with either acenocoumarol or phenprocoumon, patients were asked to fill in the BMQ questionnaire.

To compare the beliefs of coumarin users with users of other cardiovascular drugs, data from the study of van Geffen et al. were used [9]. In this study users of an antihypertensive drug or a statin were included and they all received the BMQ questionnaire by mail. Patients using a coumarin derivative were excluded from the analysis. This study included new users who did not have any antihypertensive drug or statin in the previous 2 years and chronic users who had been prescribed at least 40 prescriptions in the previous three years. More information about this study can be found elsewhere [9]. Because all coumarin users in the EU-PACT study were new users, we looked at new and chronic users in the data of van Geffen et al. separately.

Beliefs about Medicines Questionnaire

The BMQ-Specific used in this study focused on beliefs about acenocoumarol and phenprocoumon or other cardiovascular medicines. This questionnaire consists of two scales [6]. The necessity scale is focused on patients' beliefs about the necessity of using their medicines. The concerns scale is focused on the concerns that patients may have about their medicines. Each item is scored on a 5-point Likert scale: 1 (strongly disagree), 2 (disagree), 3 (uncertain), 4 (agree) or 5 (strongly agree). The scores obtained from the individual questions in each scale were summed, divided by the total number of statements in the scale and then multiplied by 5 [5]. The range of possible scores

on each scale was 5 to 25. Higher scores represented stronger necessity or concern beliefs. A necessity-concerns differential was calculated by subtracting the concerns scores from the necessity scores (range -20 to 20).

Statistical analysis

Data was analysed using SPSS version 19. Patients were excluded from the analysis if more than two answers of the BMQ were missing. Missing item scores of included patients were replaced by a score of 3 (uncertain) on the Likert-scale. To confirm the psychometric properties of this Dutch version of the BMQ used in coumarin users, a principal component factor analysis (PCA) was performed with varimax rotation. Internal consistency of different parts of the BMQ was estimated using Cronbach's alpha.

Mean and median necessity and concerns scores and the necessity- concerns differential were calculated for patients with AF and for patients with VTE. The scores for the necessity and concerns scales were split at the scale midpoint to create four belief groups: indifferent (low necessity beliefs, low concerns), accepting (high necessity beliefs, low concerns), skeptical (low necessity beliefs, high concerns) and ambivalent (high necessity beliefs, high concerns). These groups have been used in earlier studies also [5,9,10]. Chi-square tests were used to compare the percentage of patients with a specific attitude for AF and VTE patients or new and chronic users.

RESULTS

Participants

In The Netherlands, 340 patients were included in the EU-PACT trial. Of these, 20 patients did not complete the BMQ. One answer was missing (and replaced by a score of 3) in 2 (0.6%) patients, there were no patients with more than one answer missing. Table 1 shows the characteristics of the 320 patients included in this study.

Beliefs about acenocoumarol and phenprocoumon

PCA confirmed the original structure with two components for necessity beliefs and concerns. Internal consistency was similar amongst the components ($\alpha = 0.66$ for concerns and $\alpha = 0.67$ for necessity). Factor loadings are reported in Table 2.

The necessity and concerns scores and the necessity-concerns differential of acenocoumarol and phenprocoumon users are shown in Table 3. The mean necessity score for the entire population was higher than the scale midpoint (15.3) while the mean concerns score was lower than the scale midpoint (12.3). This led to a positive mean necessity-concerns differential of 3.0. The highest mean score was seen in the item 'My health, at present, depends on my coumarin'. For this item, 49.7% of the patients agreed or strongly agreed. The lowest score was seen in the item 'My coumarin disrupts my life', for which 80.3% of the patients disagreed or strongly disagreed.

Patients with AF had significantly lower necessity beliefs (14.9) than patients with VTE (16.8, $p < 0.001$). Also the necessity-concerns differential was higher in VTE patients than in AF patients (4.9 vs. 2.4, $p < 0.001$).

Table 1. Characteristics of included patients

Characteristics	EU-PACT trial (n=320)		Van Geffen study (n=493)*	
	AF (n=249)	VTE (n=71)	New users (n=301)	Chronic users (n=192)
Age in years, mean (range)	68 (37-90)	54 (22-83)	59 (19-88)	67 (39-98)
Sex, n (%)				
Male	156 (62.7%)	37 (52.1%)	149 (49.5%)	111 (57.8%)
Female	93 (37.3%)	34 (47.9%)	152 (50.5%)	81 (42.2%)
Medication, n (%)				
Acenocoumarol	119 (47.8%)	44 (62%)	-	-
Phenprocoumon	130 (52.2%)	27 (38%)	-	-
Other antithrombotic	-	-	57 (18.9%)	71 (37%)
No antithrombotic (one or more other cardiovascular drugs)	-	-	244 (81.1%)	121 (63%)
Co-morbidity				
Hypercholesterolemia	63 (25.3%)	3 (4.2%)	107 (37.5%)	101 (54.3%)
Hypertension	121 (48.6%)	14 (19.7%)	179 (61.1%)	148 (79.6%)
Diabetes	38 (15.3%)	3 (4.2%)	40 (13.7%)	74 (39.8%)
Angina pectoris	8 (3.2%)	0 (0%)	20 (7.6%)	41 (23.7%)
Myocardial infarction	21 (8.4%)	1 (1.4%)	12 (4.5)	22 (12.7)
Transient ischaemic attack	7 (2.8%)	1 (1.4%)	14 (5.3%)	15 (8.7%)
Stroke	7 (2.8%)	1 (1.4%)	11 (4.2%)	5 (2.9%)

* Coumarin users were excluded for this analysis
AF=Atrial fibrillation, VTE=Venous thromboembolism

Figure 1 shows the necessity and concerns scores of patients with VTE or with AF and the percentage of patients in each belief group. Most patients had low concerns, 85% of the patients were either in the indifferent or in the accepting group. Fifty-eight percent of the patients with VTE were accepting, versus 34% of the patients with AF (p<0.001). AF patients were more frequently in the indifferent group (51% vs. 31%, p=0.003).

Comparison with beliefs about other cardiovascular drugs

Data of 578 patients were available from the study of van Geffen *et al.* [9]. Of these, 529 patients filled in all the questions or the BMQ. One answer was missing in 18 (3.3%) patients; two answers were missing in 4 (0.7%) patients. In total, 27 patients missed more than 2 items, and these patients were excluded from the present analyses. As we wanted to compare coumarin users with users of other cardiovascular drugs (and other

Table 2. Principal component analysis using Varimax rotation.

	Concerns	Necessity
My health, at present, depends on my coumarin		0.673
Having to take coumarins worries me	0.548	
My life would be impossible without my coumarin		0.692
I sometimes worry about the long-term effects of my coumarin	0.724	
Without my coumarin I would be very ill		0.682
My coumarin is a mystery to me	0.400	
My health in the future will depend on my coumarin		0.663
My coumarin disrupts my life	0.656	
I sometimes worry about becoming too dependent on my coumarin	0.734	
My coumarin protects me from becoming worse		0.542
This coumarin has unpleasant side effects	0.566	

Factor loadings >0.30 are reported.

6

Table 3. Mean scores (median) on the BMQ-specific

	EU-PACT trial (n=320)		Van Geffen study (n=493)	
Beliefs	**AF (n=249)**	**VTE (n=71)**	**New users (n=301)**	**Chronic users (n=192)**
Necessity	14.9 (15)	16.8 (17)[a]	14.9 (15)	17.9 (18)[a]
Concerns	12.5 (12.5)	11.9 (11.7)	13.3 (13.0)	14.1 (14.0)[a]
Necessity-Concerns	2.4 (2.2)	4.9 (4.5)[a]	1.5 (1.0)	3.8 (3.5)[a]

[a] p<0.05 for AF vs. VTE or new users vs. chronic users

antithrombotics), we excluded 58 coumarin users from the van Geffen study. Table 1 shows the characteristics of the 493 patients included in the analysis of the van Geffen study. PCA with Varimax rotation resulted in the same two-component structure as in the EU-PACT study.

The necessity and concerns scores and the necessity-concerns differential of cardiovascular drug users are shown in Table 3. The mean necessity score of the entire population was higher than the scale midpoint (16.1) while the mean concerns score was lower than the scale midpoint (13.6). This led to a positive mean necessity-concerns differential of 2.4. The highest mean score was seen in the item 'My cardiovascular medicines protect me from becoming worse'. For this item, 59.2% of the patients agreed or strongly agreed. The lowest score was seen in the item 'My cardiovascular medicines disrupt my life', for which 77.7% of the patients disagreed or strongly disagreed.

Chronic users of cardiovascular drugs had significantly higher necessity scores (17.9 vs. 14.9, p<0.001), higher concern scores (14.1 vs. 13.3, p=0.046) and a higher necessity-concerns differential (3.8 vs. 1.5, p<0.001) than new users. New
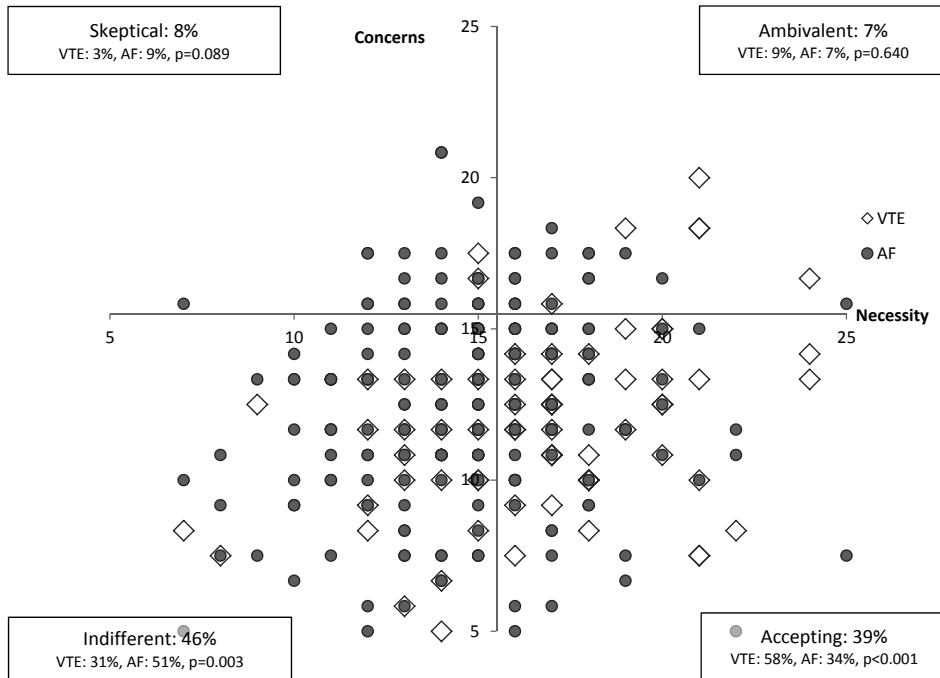
Figure 1. Scatter plot of the necessity and concerns scores by indication (Squares: venous thromboembolism (VTE), circles: atrial fibrillation (AF)). In the boxes, the percentage of VTE and AF patients that have the specific attitude towards the therapy is shown.

users of cardiovascular drugs did not have a significantly different necessity score than new users of coumarin derivatives (14.9 vs. 15.3, p=0.13). These patients did have a higher concerns score (13.3 vs. 12.3, p=0.01) and a lower necessity-concerns differential (1.5 vs. 3.0, p<0.001) than coumarin users.

Figure 2 shows the necessity and concerns scores of new and chronic users of cardiovascular drugs and the percentage of patients in each belief group. Most patients had low concerns, 69% of the patients were either in the indifferent or in the accepting group. Forty-six percent of the chronic users were accepting, versus 26% of the new users (p<0.001). New users were more frequently in the indifferent group (45% vs. 20%, p<0.001). New users of an antithrombotic were more often accepting than new users of other cardiovascular drugs (33% vs. 24%, p=0.136) and less often indifferent (32% vs. 48%, p=0.025).

DISCUSSION

Users of coumarin anticoagulants display higher necessity beliefs compared to concerns, which is also the case in users of other cardiovascular drugs. Patients with
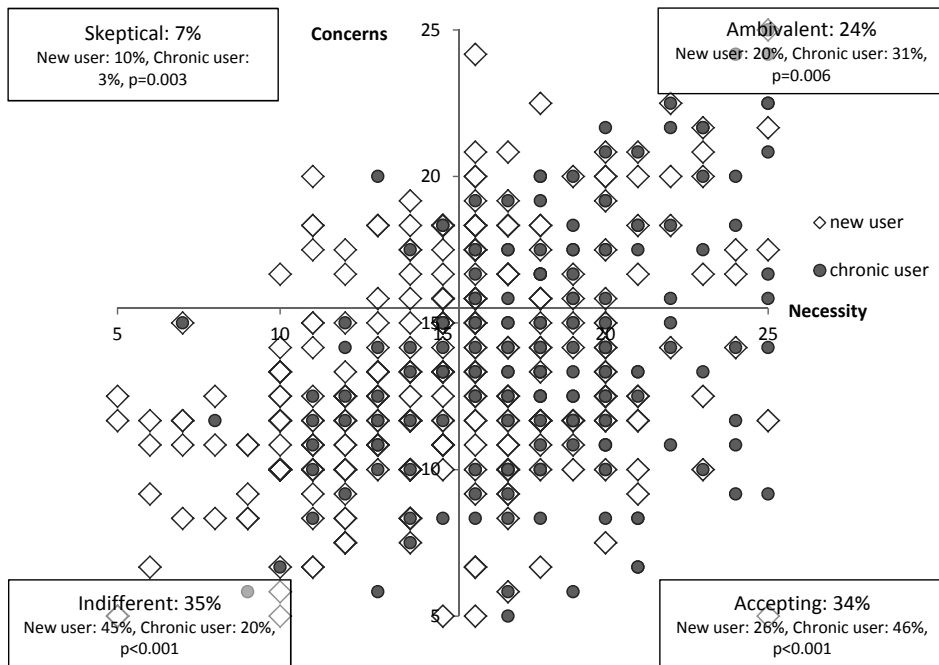
Figure 2. Scatter plot of the necessity and concerns scores by duration (Squares: new users, circles: chronic users). In the boxes, the percentage of new and chronic patients that have the specific attitude towards the therapy is shown.

VTE score higher on the necessity scale and the necessity-concerns differential than patients with AF. This is also true for chronic users of antihypertensives or statins if compared to new users of these drugs. The fact that patients score higher on the necessity scale than on the concerns scale would indicate a positive attitude towards these drugs, the most positive attitude is found in coumarin users with VTE or chronic users of cardiovascular drugs. Patients with AF have a less positive attitude and might benefit from extra attention to improve their adherence.

A possible limitation to this study is that the beliefs about coumarin derivatives were measured among patients participating in a randomised controlled trial. This could have led to a selection bias, selecting more patients with a positive attitude towards the drugs. In this trial, however, no new drug was being investigated, but a new dosing strategy. On the other hand patients with more concerns about the adverse effects of coumarin anticoagulants could have been more willing to participate, hoping that genotype-guided dosing would reduce the risk of adverse events. The study of van Geffen *et al.* was an observational study [9]. The results of the necessity and concerns scores in this study were similar to the results from the EU-PACT trial (necessity above scale midpoint, concerns

below scale midpoint, necessity-concerns differential around 3). The comparability between the two studies could also be hampered by the difference in the way the questionnaire was administered (during a visit to the anticoagulation clinic vs. over mail). The effect of data collection method on the difference between these two groups remains unclear.

To our knowledge this is the first study investigating the beliefs about coumarin derivatives. In the study by van Geffen et al., the beliefs about cardiovascular medication were investigated in relation to satisfaction with information [9]. In their study, some coumarin users were also included, but not analysed separately. In our study, the mean necessity score was above scale midpoint. This is in agreement with the necessity scores in the other studies. In a study on the beliefs about inhaled corticosteroids in the Netherlands, the necessity score was 15.6, which is similar to the score of 15.3 in the present study [5]. Necessity scores were even higher in a study on Norwegian patients with a mental disorder (17.2) [2] or in British patients with rheumatoid arthritis (19.2) [4]. In these two studies, the concerns scores were also above midpoint (17.9 and 15.8 respectively). In other studies the concerns were lower, as in the present study [3,5,11]. The necessity-concerns differential is positive in most cases, except for patients with a mental disorder in which this differential was -0.70 [2].

In many of these studies, the beliefs about medicines was shown to be related to the adherence [1-5,10]. According to Clifford and colleagues, intentional non-adherence was associated with lower necessity beliefs and higher concerns [1]. Unintentional non-adherence was not associated with the beliefs about medicines. Aikens et al. found that adherence was associated with the necessity-concerns differential and was highest in patients in the 'accepting' group (high necessity beliefs, low concerns) [10]. Most of the coumarin users with VTE are in this group (58%). Coumarin users with AF however, are more often in the 'indifferent' group (low necessity beliefs, low concerns). This could mean that patients with AF are at increased risk of poor adherence. Patients using coumarin anticoagulants for VTE generally have more complaints (pain) and therefore see the usefulness of coumarin anticoagulants more than patients using these drugs for AF. This could explain the higher necessity scores and necessity-concerns differential in this group. Although patients with AF often have complaints, these are generally controlled with rate or rhythm control. The additional antithrombotic treatment might therefore be perceived as less important. It would be interesting to look at the differences in beliefs between patients with complaints related to AF or with a previous TIA or stroke and patients without any complaints. In this study, this information was not available and the groups of patients with a previous TIA or stroke were too small to perform a subgroup analysis.

Van Geffen et al. showed that the beliefs about medicines were associated with the patients' needs for information and counselling [9]. The BMQ could be used to identify the patients who would benefit most from extra patient education. This education could address any questions they might have and dispel any misunderstanding or concerns. This could decrease the concerns and if the necessity of the treatment can be

explained clearly to the patient, this might increase the necessity beliefs.

Because warfarin is not used in the Netherlands, we did not include warfarin users in this study. However, no differences were found between the two coumarin anticoagulants investigated in this study and it is therefore likely that similar results would be seen for warfarin. The choice between acenocoumarol or phenprocoumon is in the Netherlands mainly based on the region, rather than on patient characteristics, so no selection bias is expected regarding the prescribed coumarin anticoagulant. All patients in this study attended an anticoagulation clinic, which is standard practice in The Netherlands. This might have caused a slightly different view on the drugs than patients treated by, for example, the general practitioner, because these clinics have considerable experience with the drugs and provide relevant information and education to patients. We also have no data on patients doing self-management or self-monitoring of the treatment, which could change their beliefs about the treatment. The EU-PACT study took place in a stable socioeconomic environment and patients were well educated, which might make the results less transferable to a setting where these characteristics are different. However, socioeconomic factors have not consistently been linked to either beliefs about medicines or medication adherence.

Recently, new oral anticoagulant drugs (direct thrombin inhibitors and factor Xa inhibitors) have been developed and these are considered to be good alternatives to coumarin derivatives. These new drugs do not require monitoring as is the case with coumarin anticoagulants, which could lead to a higher risk of poor adherence. However, the adherence to these drugs has not been investigated extensively yet and is still reason for concern [12]. Because the adherence in clinical trials is generally assumed to be higher than in clinical practice, the effectiveness of the new drugs could be less favourable than what is currently seen in these trials. The results of this study show that patients using coumarin derivatives generally have a positive attitude towards their therapy. Because of this positive attitude and the fact that frequent monitoring is required, the overall risk of poor adherence with coumarin derivatives is probably low. In some groups however, this risk is higher than in others (for example patients with AF, compared to VTE patients). Patients with AF could benefit from extra attention, with for example patient education.

Future studies can investigate the association of the beliefs with patient adherence in coumarin users or even with the time spent within the therapeutic INR range. The quality of INR control was shown to be associated with adherence in the past [13]. In a larger study, the correlation with age, educational levels or presence of comorbidities could also be tested, as the subgroups in this study were small. In clinical practice, the BMQ could be used as a simple tool to measure patient beliefs and subsequently identify patients with a negative attitude towards anticoagulant therapy. Knowledge of the beliefs the patient has about the medication can be taken into account during contact with patients to improve their attitude towards the treatment and possibly subsequently improve their therapy adherence.

6

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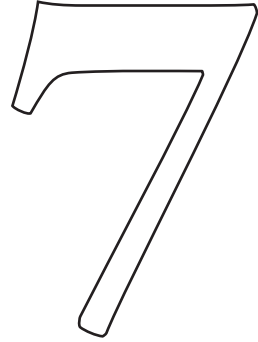
**PART II
COST-EFFECTIVENESS
OF ORAL ANTICOAGULANTS**

7

A SYSTEMATIC REVIEW OF COST–EFFECTIVENESS ANALYSES OF PHARMACOGENETIC-GUIDED DOSING IN TREATMENT WITH COUMARIN DERIVATIVES

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ABSTRACT

Anticoagulant therapy with coumarin derivatives is often sub- or supra-therapeutic, resulting in an increased risk of thromboembolic events or haemorrhage, respectively. Pharmacogenetic-guided dosing has been proposed as an effective way of reducing bleeding rates. Clinical trials to confirm the safety, efficacy and effectiveness of this strategy are ongoing, but in addition, it is also necessary to consider the cost–effectiveness of this strategy. This article describes the findings of a systematic review of published cost–effectiveness analyses of pharmacogenetic-guided dosing of coumarin derivatives. Similarities and differences in the approaches used were examined and the quality of the analyses was assessed. The results of the analyses are not sufficient to determine whether or not pharmacogenetic-guided dosing of coumarin anticoagulants is cost effective. More reliable cost–effectiveness estimates need to become available before it is possible to recommend whether or not this strategy should be applied in clinical practice.

INTRODUCTION

Coumarin derivatives are a group of oral anticoagulants used to treat and prevent thromboembolic events in patients with venous thromboembolism, atrial fibrillation or a prosthetic heart valve [1]. Among the coumarin anticoagulants, warfarin is the most commonly used, but there are differences in practice that vary across Europe, with aceno-coumarol and phenprocoumon also being used frequently [2]. Coumarin dosing requires maintenance of the international normalised ratio (INR) within a narrow range, but as there is wide interpatient variability, the required dosage is difficult to predict. This means sub- and supra-therapeutic anticoagulation levels often occur, resulting in an increased risk of (recurrent) thromboembolic events or haemorrhage, respectively [3,4]. Bleeding is a common adverse effect of coumarin anticoagulants; major bleeding events, such as intracranial haemorrhage, can cause high morbidity and mortality and are costly to manage [5].

Coumarin dose requirements and the risk of over- or under-anticoagulation are dependent on several environmental and clinical factors, such as comorbidity, concurrent medication, diet, sex and age, but genetic factors also play an important role in the variability in response among patients treated with coumarin anticoagulants [6-9]. Polymorphisms in both the *CYP2C9* gene, coding for the main metabolizing enzyme, CYP2C9, and the *VKORC1* gene, coding for the target enzyme VKORC1, are associated with coumarin dose requirements [8,10-12]. Initial studies found that patients with a *CYP2C9*2* or *3* allele variant had a lower dose requirement than patients with a wild-type variant, owing to reduced enzyme activity, and were therefore at increased risk of bleeding complications [13]. Later, it became clear that variants in the *VKORC1* allele were also responsible for increased warfarin sensitivity [14].

Currently, the initial coumarin dose is based on clinical characteristics. It has been suggested that consideration of the genotype of the patient will lead to a more appropriate initial dose and

thereby improve the safety and efficacy of therapy [10,15-17]. The results of three small randomised trials support the notion that pharmacogenetic-guided initial dosing may improve the safety and efficacy of warfarin [18-20], and more trials are planned, or are ongoing, to investigate the added value of a genotype-guided dosing algorithm against standard (or non-genotype-guided) dosing algorithms [21,22].

Although genotyping patients prior to commencing coumarin therapy might improve health outcomes, consideration of costs is also warranted. Therefore, in addition to establishing the effectiveness of this strategy, it is also necessary to consider whether or not a pharmacogenetic-guided dosing strategy is a cost-effective use of healthcare resources. Numerous economic evaluation studies have been performed in order to consider this, but these have not yet been reviewed systematically. Such a

review is necessary to see whether valuable recommendations can be made to decision-makers about this pharmacogenetic testing and whether current clinical practice should be changed or not.

The aims of this study were to systematically review and summarise the results of published economic evaluations of pharmacogenetic-guided dosing in relation to coumarin derivatives, and to identify differences and similarities among them. A further aim was to establish whether the available evidence is sufficient to recommend the implementation of pharmacogenetic-guided dosing of coumarin anticoagulants in routine practice. A comparison of the relevant studies in terms of the methodology used and their results can lead to recommendations about how economic evaluations should be designed to obtain valid and reliable estimates of cost–effectiveness.

MATERIALS & METHODS

Literature search

Search strategy

Literature was searched for relevant articles published up to November 2009 using PubMed, Embase, Web of Science and the NHS Economic Evaluation Database (NHS EED). Three categories of search terms were combined. The first category included the keywords 'coumarin*', 'anticoagulant*', 'acenocoumarol', 'phenprocoumon' and 'warfarin'. The second and third categories consisted of pharmacogenetic and pharmacoeconomic terms, respectively. All keywords were used as 'free text' terms. We did not apply a start date other than the standard start date in the databases. Papers

published in languages other than English were excluded. More details on the search strategy are provided in the Supplement. Titles and abstracts were scanned to identify relevant studies, as were the reference lists of papers assessed for inclusion. A citation search of these papers was also performed using Web of Science.

Selection criteria

Studies were included if they met the following criteria: a full economic evaluation was described (defined as a study in which both the costs and outcomes of different strategies were compared – i.e., a cost–benefit analysis, cost–utility analysis [CUA] or cost–

effectiveness analysis [CEA]), one of the comparators was pharmacogenetic-guided dosing of coumarin derivatives and the language of the article was English.

Data extraction

Data were extracted on the following study characteristics: coumarin anticoagulant, genotype of focus, comparator, patient population, country, type of economic evaluation, perspective, price year, time horizon of analysis, outcome measure and clinical events included in the calculations, discounting for costs and consequences, inputs and data sources used. Regarding the results, the differences in costs and effectiveness of genotyping versus no genotyping were collected, as were the cost–effectiveness ratios and the parameters assessed in sensitivity analyses.

Quality assessment

The quality of each study was assessed using the Drummond *et al.* ten-point checklist [23], modified for pharmacogenetic studies (Box 1), which enabled the identification of both the strengths and weaknesses of the studies' methodologies. The ten items were scored independently by two reviewers as 'yes', 'no' or 'cannot tell', and disagreements were resolved by consensus. An indication of the quality was based on the number of

Box 1. Checklist for quality assessment of economic evaluations. *Adapted from* [23].

Was a well-defined question posed in an answerable form?
- A research question that considered both costs and effects of genotype-guided dosing should have been stated

Was a comprehensive description of the competing alternatives given?
- The comparator should have been mentioned and the new strategy should have been at least briefly described

Was the effectiveness of the programs or services established?
- If the effectiveness of genotyping was established, the article should have mentioned whether this was based on studies (e.g., randomised controlled trial or meta-analysis) or on assumptions

Were all the important & relevant costs & consequences for each alternative identified?
- All relevant costs and consequences to answer the research question should have been identified

Were costs & consequences measured accurately in appropriate physical units?
- All of these costs and consequences needed to be included as well as measured accurately using the correct physical units or outcome measures

Were costs & consequences valued credibly?
- The basis for all costs and consequences used in the model should have been documented, or when a value was assumed, this should have been justified

Were costs & consequences adjusted for differential timing?
- If the time horizon was more than 1 year, discounting of costs and consequences was required

Was an incremental analysis of costs & consequences of alternatives performed?
- Differences in the costs and health effects of the genotyping strategy versus the nongenotyping strategy should have actually been determined

Was allowance made for uncertainty in the estimates of costs & consequences?
- A sensitivity analysis should have been performed, in order to examine the robustness of the models and assumptions in each study. In addition, justification should have been provided for the ranges of values that were used

Did the presentation & discussion of study results include all issues of concern to users?
- At least the findings of the sensitivity analysis and the transferability of the results should have been discussed

positive answers to the ten items. We then subjectively examined if there was a relationship between the quality of the studies and the reported results.

RESULTS

Search results

A total of 349, 2784, 185 and 27 records were identified in PubMed, Embase, Web of Science and NHS EED, respectively. One additional study was identified by searching reference lists and citation searching [24]. In total, nine met the inclusion criteria [24-32]. Figure 1, based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [33], presents the number of studies included at each step of the systematic review.

Characteristics of the selected studies

The general characteristics of the nine studies are described in Table 1. Eight examined the cost–effectiveness of pharmacogenetic testing in the USA [24-28,30-32] while the ninth examined its cost–effectiveness in The Netherlands [29]. The US-based studies focused on warfarin, while the Dutch study focused on acenocoumarol. No study on phenprocoumon was found. The earlier studies (up to 2008) considered only polymorphisms in the *CYP2C9* gene [24,26,28-30], while all studies published after 2008 assessed the economic
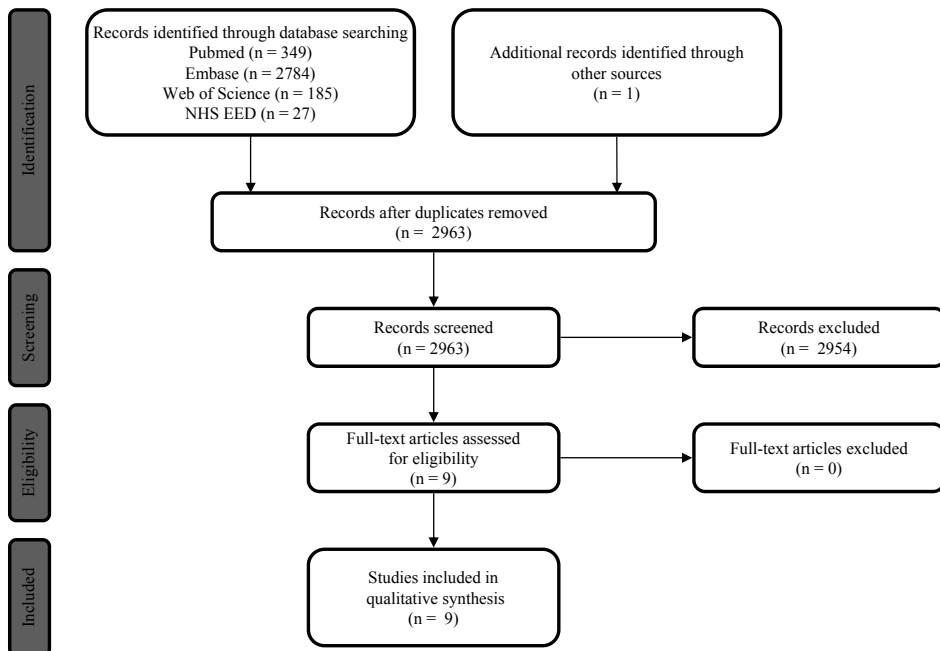
Figure 1. Literature search results

value of genotyping both *CYP2C9* and *VKORC1* [25,27,31,32].

As also shown in Table 1, all authors performed either a CEA [24,26,28-31] or a CUA [25,27,31,32]. The number of bleeding events (or adverse events) averted was the most commonly used outcome measure [24,26,28-31], followed by quality-adjusted life-years (QALYs) gained [25,27,31,32] and life-years saved [31]. Most evaluations analysed the costs from a healthcare sector perspective and used a time horizon of 12 months [24,28,30,31]. Two studies applied a societal perspective (and thus considered all costs, regardless of who would incur these costs), as well as a lifetime time horizon [25,32]. A third-party perspective was only adopted by Leey *et al.* [27]. The majority of the studies compared genotype-guided dosing with standard dosing (anticoagulation clinic) [24,25,28-32], but the comparator was not stated explicitly in two analyses [26,27]. Variation in study population was also observed. Some studies focused only on a specific patient population (e.g., patients with atrial fibrillation) [25,27,32], while other studies included all patients on coumarin therapy [24,26,28-31].

Reported results

The results of the cost analysis are presented in Table 2 & 3. Schalekamp *et al.* reported all costs in euros [29]. To increase the comparability of the results, these costs have been converted into US dollars. The price year in this study was 2004; therefore, we used a conversion rate of 1.2168 (exchange rate on 1 July 2004) [101]. The cost of genotyping varied from US$67 to US$350 for *CYP2C9* genotyping, and from US$200 to US$575 for genotyping both *VKORC1* and *CYP2C9*, and was subjected to sensitivity analysis in most instances. The cost of major bleeding or thromboembolic events was reported by most, with some authors also assessing the costs of anticoagulation service [25,30,31] or coumarin tablets and INR monitoring [25,29,32]. In total, five out of nine studies reported that a genotype-guided dosing strategy may increase healthcare costs [25,28-31]. A reduction of the relevant costs was only found in the studies by McWilliam *et al.* [24] and Leey *et al.* [27]. Leey *et al.* found that pharmacogenetic testing could reduce costs only if it reduced the risk of major bleeding, but provided no other results (i.e., specific values) regarding costs.

Estimates of the effectiveness of genotyping were derived from the literature (based on one or more randomised controlled trials [RCTs] or a meta-analysis) in some instances [25,31,32], but based on assumptions in others [29,30]. You *et al.* used data from a single RCT [31], while Patrick *et al.* applied the midpoint of the results from two RCTs [32]; Eckman *et al.* derived an estimate of effectiveness from a meta-analysis of three RCTs [25]. Leey *et al.* did not use any data for effectiveness and, instead, identified a threshold for bleeding risk at which genotyping would no longer be cost effective [27]. Another difference between the studies was the method used to estimate the clinical impact of genotyping. Some studies modelled the effect of genotyping directly on adverse event rates [24,25,27-30]. By contrast, others estimated the health effect of genotyping by estimating its impact on INR levels [31,32], since INR is known to be highly associated with the risk of (recurrent) thromboembolic events and

Table 1. General characteristics of the economic evaluations.

Study (year)	Country of focus	Price year	Drug	Genotype	Type	Perspective
Higashi *et al.* (2003)	USA	NM	Warfarin	CYP2C9	CEA	NM
You *et al.* (2004)	USA	NM	Warfarin	CYP2C9	CEA	Healthcare providers
Schalekamp *et al.* (2006)	The Netherlands	2004	Aceno-coumarol	CYP2C9	CEA	NM
McWilliam *et al.* (2006)	USA	NM	Warfarin	CYP2C9	CEA	Healthcare sector
McWilliam *et al.* (2008)	USA	NM	Warfarin	CYP2C9	CEA	Healthcare sector
Eckman *et al.* (2009)	USA	2007	Warfarin	CYP2C9 & VKORC1	CUA	Societal
You *et al.* (2009)	USA	2008	Warfarin	CYP2C9 & VKORC1	CEA & CUA	Healthcare providers
Patrick *et al.* (2009)	USA	2007	Warfarin	CYP2C9 & VKORC1	CUA	Societal
Leey *et al.* (2009)	USA	2003	Warfarin	CYP2C9 & VKORC1	CUA	Third-party payer

AC: Anticoagulation clinic; CEA: Cost–effectiveness analysis; CUA: Cost–utility analysis; NM: Not mentioned; QALY: Quality-adjusted life-year; TE: thromboembolism;
AF: atrial fibrillation

haemorrhages. In these studies, available results or assumptions regarding the relationship between genotyping and the time spent in – or outside – the therapeutic INR range were combined with the risk of clinical events at different INR levels. In the other studies, which modelled the effect of genotyping directly on adverse event rates, no information on time spent at increased risk or the time needed to reach a stable dose is described. It is possible that differences in the estimated cost–effectiveness of genotyping are partly due to differences in the methodology and assumptions used to estimate the effectiveness of genotyping.

Regarding the final economic evaluation results, most of the studies reported base case incremental cost–effectiveness ratios in the form of costs per adverse event avoided, which ranged, where reported, from dominant [24] to US$170k [31]. You *et al.* reported that genotype-guided dosing costs were US$1106k per life-year gained [31]. Costs per QALY gained (where reported) ranged from US$171k [25] to US$347k [31]. You *et al.* calculated the cost per QALY gained as well as the cost per adverse event averted and cost per life-year saved by performing both a CEA and a CUA [31]. The authors of this study included both bleeding and thromboembolic events in the definition of adverse events. By contrast, other studies reporting the cost per adverse event avoided, considered only bleeding events as adverse events, justifying this approach by stating that it was unlikely that genotype-

Time horizon	Events included	Outcome measure	Comparator	Specific patient population	Ref.
NM	Bleeding	Bleeding event averted	NM		[26]
12 months	Major bleeding, major TE	Bleeding event averted	Standard AC care	Patients newly started on warfarin therapy	[30]
12 months	Major bleeding	Bleeding event averted	Standard AC care		[29]
12 months	Bleeding, stroke	Bleeding and stroke events averted	Standard AC care		[24]
12 months	Bleeding, stroke	Bleeding events averted	Standard AC care		[28]
Lifetime	Major bleeding, TE	QALY gained	Standard care	Nonvalvular AF patients	[25]
12 months	Major bleeding, major TE	QALY gained, adverse event averted and life-year saved	Standard care	Patients newly started on warfarin therapy	[31]
Lifetime	Haemorrhagic events, ischaemic stroke	QALY gained	Standard AC care	Newly diagnosed AF patients	[32]
12 months	Major bleeding, embolic stroke	QALY gained	NM	Elderly patients newly diagnosed with AF	[27]

guided dosing would affect the risk of other adverse events, such as thromboembolic events. Instead of reporting incremental analyses, Patrick et al. reported how much of an increase (compared with usual care) in percentage time spent in the target INR range during the first 3 months of therapy would be needed in order for genotype-guided dosing to be cost effective [32]. They found that a 5% increase would be needed for the incremental cost–effectiveness ratio (ICER) to be less than US$100,000 and a 9% increase would be needed for the ICER to be less than US$50,000 per QALY gained.

Consideration of uncertainty

Table 4 presents the various parameters implemented in the sensitivity analyses. Univariate (one-way) or multivariate (two-way and three-way) sensitivity analyses were performed in all studies other than Higashi et al., which was a rudimentary analysis intended to illustrate the concepts of economic evaluation of pharmacogenetic testing [26]. Their description of the study is brief, and the authors did not perform any sensitivity analysis. In the other eight studies, a range of factors were included in sensitivity analyses; all included major bleeding event rates and consistently found that a higher baseline bleeding risk would improve the cost–effectiveness of genotype-guided dosing [24,25,27-32]. Seven of the eight studies considered the effectiveness of the genotype-guided strategy and the cost of genotyping; the only exception was Leey et al., who only varied the incremental effectiveness (i.e., difference in QALYs) but did not vary the costs of genotyping [27]. As

Table 2. Inputs of the economic evaluations

Study (year)	Baseline risk of bleeding with standard care	Baseline risk of thromboembolic event with standard care	Inputs used				
			Estimate of effectiveness	Cost of genotyping (US$)	Cost of bleeding (US$)	Cost of thromboembolic event (US$)	Ref.
Higashi et al. (2003)	0.057†/0.133‡	NA	Relative risk of bleeding incidence: 0.43§	135§			26
You et al. (2004)	0.056†/0.125‡	0.024	Odds ratio of bleeding events compared with standard care: 0.8#	100¶	11,635	10,376	30
Schalekamp et al. (2006)	0.0416†/0.068‡	NA	Relative risk of bleeding incidence: 0.8#	67¶	12,925	NA	29
McWilliam et al. (2006)	0.126†/0.276‡	††	Relative risk of bleeding incidence: 0.46§ / Relative risk of stroke incidence: 0.5#	350¶	13,500	39,500	24
McWilliam et al. (2008)	0.01–0.05	‡‡	Relative risk of bleeding incidence: 0.43§ / Relative risk of stroke incidence: 0.9 or 0.99 or 1#	250¶	19,000	42,000	28
Eckman et al. (2009)	0.001	0.014	Relative risk of bleeding incidence: 0.68	400§§	18,904–32,787¶¶	22,223	25
You et al. (2009)	0.014##	0.013##	Relative percentage reduction of out-of-range INRs: 7.3	200§§	17,414–25,660¶¶	22,079	31
Patrick et al. (2009)	0.038–0.993†††	0.077–0.006†††	Absolute increase in percentage in range: 8.5	575§§	183–33,218¶¶	21,537–15,499¶¶	32
Leey et al. (2009)	0.072	0.023		250§§	112,302–193,804¶¶	380,355	27

†Bleeding rate in patients with wild-type CYP2C9. ‡Bleeding rate in patients with variant CYP2C9. §Assumed that the adverse event rate in the variant group could be reduced to the adverse event rate in the normal group. ¶Cost for genotyping CYP2C9 only. #Assumed value. ††Number of preventable strokes: 40,000. ‡‡Number of preventable strokes: 60,000. §§Cost for genotyping CYP2C9 and VKORC1. ¶¶Various across different types of bleeding/thromboembolic events. ##In in-range INRs. †††Various across different INR ranges.
INR: International normalised ratio; NA: Not applicable

Table 3. Results of the economic evaluations

Study (year)	Effectiveness results			Cost results	Cost-effectiveness results			Ref.
	Adverse event reduction	Mortality reduction	QALY gained	Change in cost (US$)	Cost per adverse event avoided (US$)	Cost per life saved (US$)	Cost per QALY gained (US$)	
Higashi et al. (2003)					5940	NA	NA	[26]
You et al. (2004)	0.009 bleeds averted	NA	NA	+52	5778	NA	NA	[30]
Schalekamp et al. (2006)	0.49%	NA	NA	+25.46	5151	NA	NA	[29]
McWilliam et al. (2006)	Not stated directly	NA	NA	(>500 savings)	Dominant	NA	NA	[24]
McWilliam et al. (2008)	0.50%	NA	NA	+70	13,589	NA	NA	[28]
Eckman et al. (2009)	NA	NA	0.0021‡	+369‡	NA	NA	171,750	[25]
You et al. (2009)	0.000104 events averted	0.00016 deaths averted	0.00051	+177	170,792	1,106,250	347,059	[31]
Patrick et al. (2009)	NA	NA	NM	NM	NA	NA	NM†	[32]
Leey et al. (2009)	NA	NA	NM	'can reduce costs'	NA	NA	NM	[27]

†ICER <US$100,000 per QALY gained if the time spent in the target INR range during the first 3 months of treatment is increased by 5% compared with usual care, and an ICER of <US$50,000 per QALY gained if time in range is increased by 9%.
‡3% discounting.
ICER: Incremental cost–effectiveness ratio; INR: International normalised ratio; NA: Not applicable; NM: Not mentioned; QALY: Quality-adjusted life-year.

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Table 4. Sensitivity analyses used in the literature

Study (year)	Type	Prevalence of polymorphism	Major bleeding event rates	Thrombo-embolic event rates	Utilities	Effectiveness of genotyping	Accuracy of genotype testing	Cost of genotyping	Cost of major bleeding	Cost of thrombo-embolic event	Ref.
You et al. (2004)	Uni/Multi	+	+	+		+		+	+	+	30
Schalekamp et al. (2006)	Multi	-	+			+		+	+		29
McWilliam et al. (2006)	Uni/Prob	-	+	-		+	+	+	-	-	24
McWilliam et al. (2008)	Multi/Prob	-	+	-		+	-	+	-	-	28
Eckman et al. (2009)	Uni/Multi/Prob	+	+	+	-	+		+	-	-	25
You et al. (2009)	Multi/Prob		+	+	+	+		+	+	+	31
Patrick et al. (2009)	Uni/Multi/Prob		+	+	+	+		+	+	+	32
Leey et al. (2009)	Uni		+	-	-			-	-	-	27

Empty cells represent the situation in which the parameter is not included in the sensitivity analysis but also not used as an input parameter in the cost–effectiveness analysis.

+: Included in sensitivity analysis;

–: Measured, but not included in sensitivity analysis;

Multi.: Multivariate analyses; Prob.: Probabilistic sensitivity analysis; Uni.: Univariate analysis.

expected, increased effectiveness and lower costs of genotyping both improved the cost–effectiveness of a genotype-guided strategy versus standard care. The accuracy of the genotyping method was only assessed in the two studies by McWilliam *et al.* [24,28]. McWilliam *et al.* assumed that both the test specificity and test sensitivity were 95% [24], while McWilliam *et al.* assumed that both were 99% [28].

In five studies [24,25,28,31,32], a probabilistic sensitivity analysis was also performed, whereby the values of many input parameters were sampled from distributions simultaneously. This approach makes it possible to calculate the probability that the strategy is cost effective given a particular threshold willingness to pay (e.g., a maximum of US$50,000 to gain one QALY). The probability that genotype-guided dosing would be cost effective given a threshold of US$50,000 varied from 10% [25] to 38% [31] and 42% [32].

Quality of the economic evaluations
The economic analyses were of variable quality (Table 5). As mentioned earlier, data on the effectiveness of genotyping were not always derived from the literature [25,31,32], but in some instances based on assumed values [29,30].

Discounting for costs and consequences (at an annual rate of 3%) was applied in the two studies that reported a lifetime horizon of analysis [25,32]. This adjustment is not needed when the time horizon of the study is no more than 1 year. However, You *et al.* also reported using a discount rate of 3%, while the reported time horizon was only 12 months [31].

Owing to lack of detail, some items of the quality checklist were answered with some uncertainty. For example, it is likely that Leey *et al.* performed an incremental analysis, even though the results were not presented as such in the article [27]. Higashi *et al.* did not contain all elements of a full economic evaluation, since the purpose of their analysis was to illustrate how the cost–effectiveness of genetic tests could be assessed [26]. As a consequence, their article scored poorly on the checklist. Studies of high quality were the studies of Eckman *et al.* [25], You *et al.* [31] and Patrick *et al.* [32]. Based on this quality assessment, there seems to be no clear relationship between the quality of the studies and the reported results. You *et al.* reported different results from Patrick *et al.* [32] and Eckman *et al.* [25], and this might be owing to the fact that they used a 12-month time horizon instead of a lifetime horizon, but this may also be because of other reasons, such as differences in effectiveness estimates [31]. One could argue that a 12-month time horizon could underestimate the potential health gain from genotyping, since it would ignore the long-term impact of major clinical events that occur during the first year of anticoagulation.

DISCUSSION

There is considerable variation in the results of existing economic evaluations of genotype-guided dosing of coumarin derivatives. Most studies indicate that a genotype-guided dosing strategy leads to improved health outcome, but at higher cost than usual care.

Table 5. Quality assessment based on the Drummond checklist.

Study (year)	Well-defined question posed?	Description of competing alternatives given?	Effectiveness established?	Costs and consequences identified?	Costs and consequences measured accurately?	Costs and consequences valued credibly?	Costs and consequences adjusted?	Incremental analysis performed?	Allowance made for uncertainty?	Include all issues of concern?	Ref.
Higashi et al. (2003)	No	No†	Assumed	No	No	No	No (not needed)‡	No	No	No	26
You et al. (2004)	Yes	Yes	Assumed	Yes	Yes	Yes	No (not needed)‡	Yes	Yes	Yes	30
Schalekamp et al. (2006)	Yes	Yes	Assumed	Yes	Yes	Yes	No (not needed)‡	Yes	Yes	Yes	29
McWilliam et al. (2006)	Yes	No†	Assumed	Yes	No	No	No (not needed)‡	Yes	Yes	No	24
McWilliam et al. (2008)	Yes	No†	Assumed	Yes	Yes	No	No (not needed)‡	Yes	Yes	No	28
Eckman et al. (2009)	Yes	Yes	Meta-analysis	Yes	Yes	Yes	Yes§	Yes	Yes	Yes	25
You et al. (2009)	Yes	Yes	RCT¶	Yes	Yes	Yes	Yes§	Yes	Yes	Yes	31
Patrick et al. (2009)	Yes	Yes	RCT# and assumptions	Yes	Yes	Yes	Yes§	Yes	Yes	No	32
Leey et al. (2009)	Yes	No†	Assumed	No	Yes	Yes	No (not needed)‡	Yes	No	No	27

†Higashi and Leey did not explicitly state the comparator. McWilliam did not describe the new strategy sufficiently. ‡Adjustment is only necessary when the time horizon is over 1 year. §Discount rate 3%. ¶The change in INR control values is derived from a RCT, the association between INR control and adverse event rates is derived from a meta-analysis. #Time spent in target INR range measured as the midpoint of the results of two RCTs, INR-specific bleeding rates obtained from one study. INR: International normalised ratio; RCT: Randomised controlled trial. Adapted from (23).

However, a direct comparison of cost–effectiveness among studies is hampered by variability in methodology (e.g., economic outcome measure, perspective and currency), clinical considerations (e.g., consideration of thromboembolic events and genotypes) and parameter estimation (e.g., cost of genotyping and source of evidence on effectiveness).

A significant limitation of the analyses is the choice of measure of cost–effectiveness. This will influence the results; for instance, it is highly likely that the cost per life-year saved by genotype-guided dosing will be higher than the cost per adverse event avoided. You *et al.* is the only study to report on all three outcome measures (cost per bleeding event averted, life-year gained and QALY gained) [31]. Schalekamp *et al.* estimated the cost per bleeding event averted to be €4233 (US$5151), and compared this with a payer's willingness to pay up to €20,000 (US$24,336) per QALY gained [29]. However, as the denominators differ, and willingness to pay might not apply to other settings (e.g., USA is US$50,000–100,000 per QALY gained [34]), the results are not readily interpretable.

A second important difference among the studies is the values of the input parameters used in the analyses. For instance, the base case values for genotyping costs vary by more than tenfold. However, this variation alone cannot explain the difference in cost–effectiveness estimates across the studies. One critical factor that affected the results was the substantial uncertainty in the effectiveness of genotyping in reducing the risk of haemorrhage or thromboembolic events. In almost half of the studies,

effectiveness was based on assumptions and not on clinical data. For the studies that considered clinical data, data were derived from only a few small clinical trials [25,31,32]. The limitations of a lack of evidence on the effectiveness of genotyping have also been reported by Hughes *et al.* [35]. Without such information, no definitive conclusions can be made about the cost–effectiveness of this strategy.

The effectiveness of genotyping, as well as the baseline rate of bleeding events, might differ between populations, based for example on age or racial ancestry [36]. In our review, we found that some studies focused only on patients with a specific clinical indication (atrial fibrillation) [25,27,32], while other studies included all types of indications [24,26,28-31]. Schalekamp *et al.* took a different approach and examined the cost–effectiveness of genotyping only patients with an initial INR of 2.5 or higher on the fourth day of therapy. They concluded that genotyping this subgroup only seemed to be more cost effective than genotyping every patient [29]. Another way to distinguish patient subgroups would be to consider the total duration of anticoagulation therapy. Maybe patients receiving anticoagulation for a shorter period of time (e.g., patients with venous thromboembolism) would obtain more benefit from genotyping than other patients (e.g., patients with atrial fibrillation). That is, one could argue that the proportion of time spent trying to achieve a stable INR is much greater in patients with venous thromboembolism than it is in patients with atrial fibrillation, since the latter are usually treated with coumarin derivatives for a much longer

period. This might lead to the conclusion that the benefit of genotyping would be greater for patients with venous thromboembolism. However, the absolute amount of time spent trying to achieve a stable INR does not differ between these two groups. Since the absolute differences in time will determine the absolute differences in risk of clinical events, the total duration of anticoagulation therapy will not affect the effectiveness and cost–effectiveness of a genotyping strategy.

The studies assessed in this review used different data inputs, different analytic decision models and different assumptions. It is therefore difficult to determine what exactly causes the differences in ICERs across the studies. The effectiveness results of the only study that did not focus on warfarin (but on acenocoumarol) fall within the range of results of the warfarin studies [29]. The different cost–effectiveness results can also not be explained by differences between countries, since eight of the nine studies focused on the USA.

The quality of the studies varied considerably. Some studies were poorly documented and difficult to appraise [27]. A limitation of this review, therefore, is the fact that the quality of reporting might preclude judgment on the quality of the economic evaluation. The study by Higashi *et al.* scored poorly in our quality assessment, but the authors never presented it as a fully-fledged economic evaluation in the first place [26]. Instead, the study was included in their article as an illustration of the concepts of an economic evaluation of pharmacogenetic testing. Even though their paper did not address all the elements of a full economic evaluation, we still found it useful to include it in this review. In fact, it described the very first economic evaluation on this subject and gave an initial indication of the cost–effectiveness of genotyping warfarin patients.

Together, the evidence to date does not allow for a conclusion to be drawn on whether or not genotype-guided dosing is cost effective. It is therefore not possible to confirm whether or not pharmacogenetic-guided dosing should be applied in routine clinical practice. Although the US FDA has already changed the label of warfarin, promoting the use of pharmacogenetic tests [102], many would recommend delaying any decision regarding applying this strategy in clinical practice until more effectiveness data and reliable estimates of cost–effectiveness become available [35].

The quality of economic evaluations in other therapeutic areas has tended to improve over time [37,38] as more evidence becomes available. The limitations identified in this review, and differences among the selected studies, can assist in the design of future economic evaluations. We propose the following recommendations. First, effectiveness data used for the economic evaluation should be based on large RCTs, to eliminate confounding factors and reduce bias and uncertainty around any estimates of effectiveness. Second, the total cost associated with genotyping should be better established. These may be better approximated alongside a clinical trial. For example, reliable cost estimates for adverse events associated with warfarin use were calculated by Jorgensen *et al.*, using a microcosting analysis as part of a prospective cohort study [39]. Valid cost estimates will vary across different

genotyping strategies and treatment settings (e.g., hospital, general practitioner or anticoagulation clinic). Third, it is important to overcome the difficulties that arise when different studies use different outcome measures. The results of different economic evaluations are more readily comparable if the results are reported using the same outcome measures. Future economic evaluations of a genotype-guided dosing strategy for coumarin derivatives should report either the cost per QALY gained and/or the cost per life-year gained [40]. QALYs should be estimated by using utility scores based on a preference-based method (e.g., the EQ-5D™; EuroQol Group, Rotterdam, The Netherlands) [41]. Additional recommendations for consideration in the design of economic evaluations in relation to venous thromboembolism prophylaxis, including the use of a lifetime time horizon to account for the thromboembolic death and bleeding events, have been highlighted by Wolowacz *et al.* [41]. Other recommendations relate to choice of clinical events, choice of comparator, model input (efficacy and safety data and utility weights), and reporting of results.

CONCLUSION

The results of published economic evaluations on the cost–effectiveness of genotype-guided dosing in treatment with coumarin derivatives are not sufficient to determine whether or not this strategy is cost effective. Before reliable cost– effectiveness studies can be performed, more evidence about the effectiveness of genotyping is required, and the cost associated with a genotyping strategy should be defined and measured more precisely.

FUTURE PERSPECTIVE

More information on effectiveness and costs of this strategy should be made available before any recommendations can be made about whether or not a genotype-guided dosing strategy should be implemented. Obviously, it is impossible to obtain perfect evidence, but it is not clear what level of evidence is enough to make a decision about the implementation of a pharmacogenetic test. Therefore, value of information (VOI) analyses should be performed to establish the cost–effectiveness of further research on the efficiency of the strategy. If the costs of performing this research are greater than the benefits of the additional information, it would not be worthwhile to conduct this research [42]. Future studies should concentrate on collecting more data on the input parameters that have the greatest influence on the uncertainty regarding the cost–effectiveness of genotyping. These parameters include: the effectiveness of genotyping on the incidence of (recurrent) thromboembolic events; the effectiveness of genotyping on the incidence of bleeding events, and the costs associated with genotyping. The costs of conducting such research should also be considered.

Randomised controlled trials to establish the effectiveness of genotype-guided dosing in treatment with coumarin derivatives are currently underway [21,22]. Most of these studies will only investigate the effectiveness of genotyping before treatment with warfarin [22,103]. The European Pharmacogenetics of Anticoagulation Therapy (EU-PACT) trial will investigate the effect of genotyping in treatment with warfarin as well as in treatment with acenocoumarol and phenprocoumon [21]. The results of these trials will provide the necessary evidence about the effectiveness of a genotyping strategy to make it possible to conduct sufficiently valid and precise economic evaluations.

This will be possible in 3–4 years from now, because the two largest trials, the Clarification of Optimal Anticoagulation through Genetics (COAG) study [103] and the EU-PACT trial [21], are scheduled for completion in 2012 and 2013, respectively.

The trials that are currently underway will investigate the effectiveness of genotyping and will be performed independent of any VOI analyses being performed. However, when the results of these studies are available, or when new studies are being planned on the efficiency of this strategy, the VOI analyses can be very useful to establish the cost–effectiveness of performing economic evaluations on this subject.

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SUPPLEMENT

Search strategy

The following search strategy was used in all databases to find relevant articles. Search terms 1 to 5 were used to identify studies of coumarin derivatives. Terms 6 to 9 were used to identify studies of genotype-guided dosing and terms 10 to 27 were used to find economic evaluations. Lastly, the results from these three categories were combined in steps 28 to 31.

Search terms

1. coumari*
2. anticoag*
3. acenocoum*
4. phenproc*
5. warfarin*

6. pharmacogenet*
7. genetic*
8. screen*
9. genot*

10. economics
11. econom*
12. costs
13. costly
14. costing
15. price
16. prices
17. pricing
18. pharmacoeconomics
19. pharmacoecon*
20. budget*
21. expenditure*
22. energy
23. 21 not 22
24. "value for money"
25. cost-eff*
26. cost-ben*
27. cost-util*

28. 1 or 2 or 3 or 4 or 5
29. 6 or 7 or 8 or 9
30. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 23 or 24 or 25 or 26 or 27

31. 28 and 29 and 30
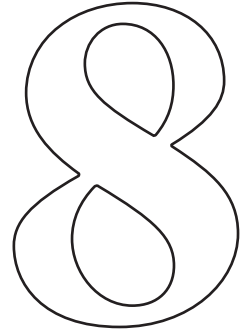
CLINICAL AND ECONOMIC CONSEQUENCES OF PHARMACOGENETIC-GUIDED DOSING OF WARFARIN

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ABSTRACT

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.

INTRODUCTION

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 normalised 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 randomised 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 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 reanalysed 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 individualised 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 personalised. 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 Warfarin 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.

8

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WEBSITE

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

9

COST-EFFECTIVENESS
OF PHARMACOGENETIC-GUIDED DOSING
OF PHENPROCOUMON IN ATRIAL FIBRILLATION

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Anke-Hilse Maitland-van der Zee
on behalf of the EU-PACT group

ABSTRACT

Objectives: To investigate the cost–effectiveness of pharmacogenetic-guided phenprocoumon dosing versus standard anticoagulation care in Dutch patients with atrial fibrillation.

Methods: Using a decision-analytic Markov model, cost–effectiveness of pharmacogenetic-guided therapy versus standard care was estimated.

Results: Compared with standard care, the pharmacogenetic-guided dosing strategy increased quality-adjusted life-years (QALYs) only very slightly and increased costs by €15. The incremental cost–effectiveness ratio was €2658 per QALY gained. In sensitivity analyses, the cost of genotyping had the largest influence on the cost–effectiveness ratio. In a probabilistic sensitivity analysis, the incremental costs of genotype-guided dosing were less than €20,000 per QALY gained in 75.6% of the simulations.

Conclusions: Pharmacogenetic-guided dosing of phenprocoumon has the potential to increase health slightly and may be able to achieve this in a cost-effective way. Owing to the many uncertainties it is too early to conclude whether or not patients starting phenprocoumon should be genotyped.

INTRODUCTION

Coumarin derivatives are widely used anticoagulants, prescribed to treat and prevent thromboembolic events, in patients with, for example, atrial fibrillation [1,2]. Warfarin is the most commonly used coumarin anticoagulant, but in several European countries phenprocoumon or acenocoumarol are more frequently used [3]. Warfarin, acenocoumarol and phenprocoumon have a similar mechanism of action, but phenprocoumon has a longer elimination half- life (110–130 h vs. 24–58 h for warfarin and 2–7 h for acenocoumarol) [4]. Treatment with coumarin derivatives is challenging owing to a narrow therapeutic range and large variability in dose–response among users, which can result in under- or over-anticoagulation [5]. Under-anticoagulation is associated with treatment failure, an increased risk of thromboembolic events; over-anticoagulation is associated

with an increased risk of bleeding [6]. Major bleeding events, such as intracranial haemorrhage or gastrointestinal bleeds can be life-threatening and are costly to manage [7]. The anticoagulant effect of coumarins should therefore be monitored frequently by measuring the prothrombin time, commonly expressed as the International Normalised Ratio (INR; ratio of patient prothrombin time to a control sample). The target INR range for atrial fibrillation is normally 2.0–3.0. In some countries a slightly different range is used, such as in The Netherlands, where a therapeutic INR range of 2.0–3.5 is used [8].

The variability in dose requirements can be explained by several factors such as age, sex, height, weight, concomitant medication, diet and genetic factors [4]. Polymorphisms in the *CYP2C9* and *VKORC1* genes together

explain approximately one-third of the variation in coumarin dose requirements [9,10]. The *CYP2C9* gene codes for the main metabolizing enzyme of coumarin anticoagulant, CYP2C9, and the *VKORC1* gene codes for the target enzyme, VKORC1. Information about a patient's genotype could thus be used to guide the coumarin dose before treatment initiation, thereby increasing the safety and effectiveness of the treatment [11,12]. Some small clinical trials have already investigated the effectiveness of this pharmacogenetic-guided dosing [13-16] and larger trials are underway [17-19].

In addition to effectiveness, the cost–effectiveness of genotyping should be considered before implementation in clinical practice. Several authors have investigated this for warfarin and the most recent study was published in 2010 by Meckley *et al.* [20]. These authors studied the cost–effectiveness of warfarin pharmacogenetic-guided dosing using the INR as a validated surrogate measure for the risk of bleeding and thromboembolic events. The cost–effectiveness of genotype-guided dosing of acenocoumarol in The Netherlands has been studied by Schalekamp *et al.* [21]. However, to our knowledge, no studies have examined the cost–effectiveness of genotyping patients initiating phenprocoumon. The aim of this study was to investigate the cost–effectiveness of pharmacogenetic-guided phenprocoumon dosing versus standard anticoagulation care in Dutch patients with atrial fibrillation. This indication is the most important indication for coumarin anticoagulants and these patients frequently need lifelong treatment.

MATERIALS & METHODS

Model structure

A decision-analytic Markov model was developed by Meckley *et al.* to analyse the cost–effectiveness of pharmacogenetic-guided dosing for warfarin [20]. This model was used as a basis for the analyses in our study and adapted in several ways, as discussed in the next section. The model was developed using Tree- Age software (TreeAge Pro 2012). The model was used to compare the incidence of adverse events, quality-adjusted life-years (QALYs), and direct medical costs of pharmacogenetic-guided phenprocoumon therapy (PGx) versus standard phenprocoumon therapy over a lifetime horizon. In The Netherlands, standard phenprocoumon therapy is managed by anticoagulation clinics. After the treatment is initiated with a standard loading dose, the INR is measured and the dose can be adapted by specialised physicians afterwards.

Data from the pre-EU-PACT study were used to populate the decision-analytic Markov model [12]. In this study, patient-level data regarding age, INR values, therapy indication, and *CYP2C9* and *VKORC1* genotype of 624 patients receiving standard phenprocoumon therapy were collected. The base-case analysis consisted of a hypothetical cohort of patients with atrial fibrillation, aged 71.5 years (mean age at start of therapy for atrial fibrillation in the pre-EU-PACT study [12])

initiating phenprocoumon therapy. Figure 1 shows the decision tree with the two strategies, PGx versus standard care. Patients were first stratified by *VKORC1* genotype, because this gene has the largest influence on INR variation [12]. Patients in each of the *VKORC1* genotype groups were then further stratified by *CYP2C9* genotype. The *CYP2C9* wild-type group consisted of *1*1 patients, and carriers of at least one *2 or *3 allele were classified as variant carriers.

The decision-analytic Markov model consisted of six Markov states: atrial fibrillation with no adverse event, no adverse event plus stop therapy, major bleeding event (bleed), thromboembolic event, sequelae and death. All patients entered the model in the 'healthy with atrial fibrillation' state and could move to other states at monthly intervals (Figure 2). Major bleeds were classified as an intracranial haemorrhage (ICH) or a gastrointestinal (GI) bleed, since the majority (89%) of extracranial haemorrhages are GI bleeds [22]. A total of 16% of the major bleeds in The Netherlands were ICH [101] and we assumed that the other (extracranial) bleeds were GI bleeds. Patients with a GI bleed were assumed to recover after 1 month, while patients with an ICH had a 44% chance of dying [101] and 50% chance of recovery with sequelae [22]. The remaining patients (6%), who experienced an ICH and subsequently
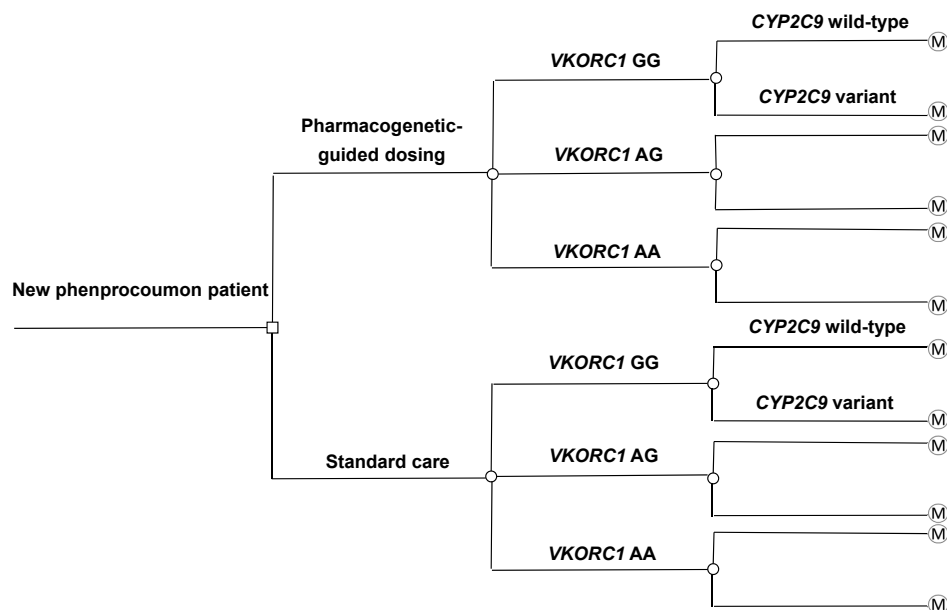
Figure 1. Model structure of the decision tree used to analyse the cost–effectiveness of pharmacogenetic-guided dosing versus standard care. Patients initiating treatment with phenprocoumon are classified according to treatment arm (pharmacogenetic- guided dosing or standard care) and stratified by genotype. The two arms are equal up to the Markov node. At this point, different chances of developing adverse events are defined. M: Markov nodes.
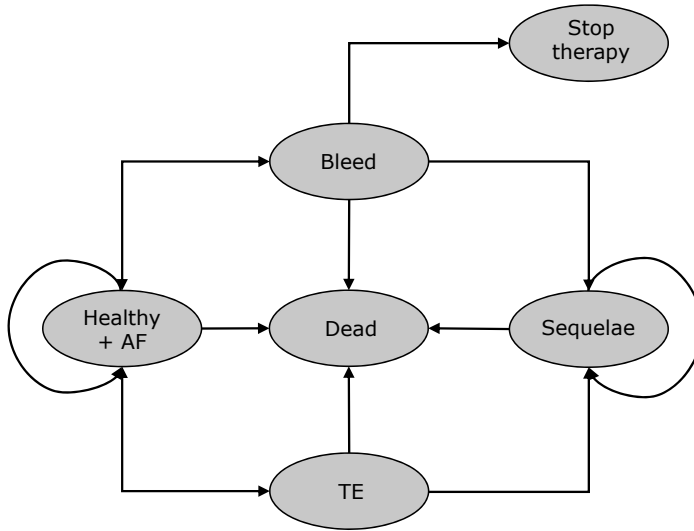
Figure 2. Markov model health states. All patients enter the model in the 'healthy + AF' state and can move to other states at monthly intervals. AF: Atrial fibrillation; TE: Thromboembolic event.

fully recovered, were assumed to stop phenprocoumon therapy as a result. A total of 60% of the thromboembolic events were classified as ischaemic stroke and the remainder (40%) as transient ischaemic attack (TIA). Stroke and TIA represent the main therapeutic effect of phenprocoumon. In order to prevent the model from being too complicated, we decided not to include other cardiovascular events, such as myocardial infarction or angina pectoris, and invasive interventions, such as coronary bypass surgery or percutaneous coronary interventions, but focus on the main therapeutic effect only. We assumed that 11% of the patients with a stroke died within 1 month [101], 47% recovered with sequelae [20] and the remainder fully recovered within 1 month. All patients with a TIA were assumed to be fully recovered the next month. Age-specific mortality rates were taken into account for all

patients. Input parameters of the model are shown in Table 1. Utilities and disutilities of the different health states and the cost parameters are shown in Table 2.

Clinical input

An INR measure such as time in therapeutic range is commonly used as the primary outcome in clinical trials investigating the effect of genotyping because of the relatively low rate of adverse events [13,16,17,20]. The percentage time in different INR ranges was therefore used to determine the probability of an event for each of the genotype subgroups. The average percentage time spent in the four different INR ranges, <2.0; 2.0–3.5; >3.5–5.0 and >5.0 was determined for each genotype subgroup from data of the pre-EU-PACT study, which was assumed to reflect the standard phenprocoumon treatment in The Netherlands. The percentage time in

different INR ranges was calculated using the method of Rosendaal *et al.* [23] with Predictive Analytics Software Statistics (PASW Statistics) software, version 18. Figure 3 depicts the percentage time spent in the different INR ranges during the first and sixth month of phenprocoumon treatment in the different *VKORC1* (GG, GA and AA) and *CYP2C9* (wild-type or variant carrier) genotypes. It was assumed that this percentage is stable from month 12 of anticoagulation therapy. The risks of adverse events associated with each of the four INR ranges were derived from the meta-analysis by Oake *et al.* [24]. In this study

the risk of bleeding or thromboembolic events was investigated for four INR ranges (<2.0; 2.0–3.0; >3.0–5.0 and >5) where the target range was 2.0–3.0. We assumed that the risk of an adverse event associated with an INR in this target range was similar to the risk with an INR in the 2.0–3.5 target range used in The Netherlands.

The increased risk of thromboembolic events at INR levels >5 is different from what would be expected. According to Oake *et al.*, this reflects a curvilinear association between INR levels and thromboembolic event risk, which is found in several studies in their meta-analysis [24]. This association
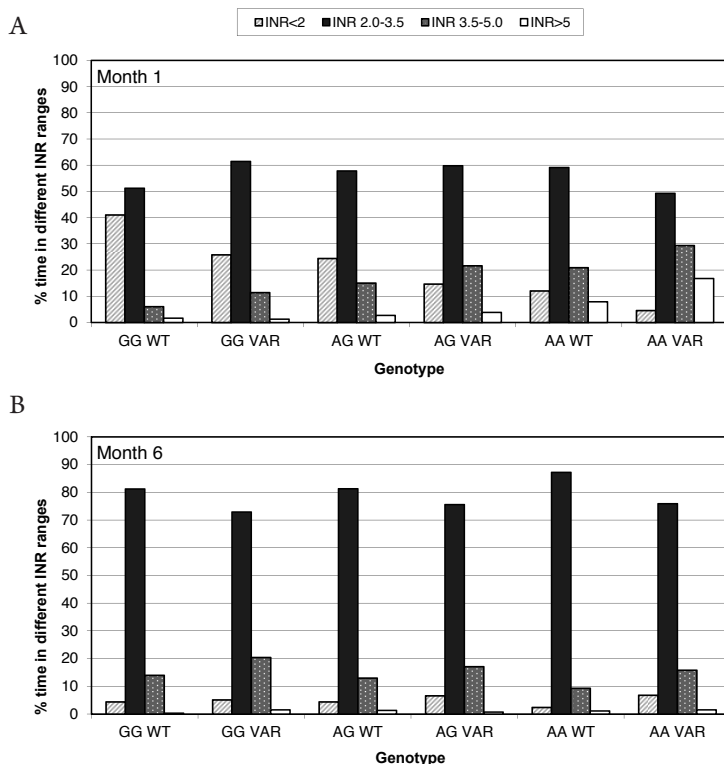
Figure 3. Percentage time spent in different International Normalised Ratio ranges during the first and sixth month of standard phenprocoumon treatment. *VKORC1* genotype is shown (GG, AG, AA), as well as *CYP2C9* genotype (WT or VAR). INR: International Normalised Ratio; VAR: Variant; WT: Wild-type.

Table 1. Input parameters used in the model

Parameter	Base case	Range	Source
Age at start of treatment (years)	71.5	51.9 to 91.1†	Pre-EU-PACT (Verhoef et al, unpublished data)
Genotype (%)			
VKORC1 GG (wild-type)	0.373	0.329 to 0.419†	Pre-EU-PACT (Verhoef et al, unpublished data)
VKORC1 GA	0.472	0.426 to 0.519†	Pre-EU-PACT (Verhoef et al, unpublished data)
VKORC1 AA	0.155	0.123 to 0.191†	Pre-EU-PACT (Verhoef et al, unpublished data)
CYP2C9 wild-type	0.669	0.624 to 0.711†	Pre-EU-PACT (Verhoef et al, unpublished data)
CYP2C9 variant	0.331	0.289 to 0.376†	Pre-EU-PACT (Verhoef et al, unpublished data)
Risk of bleeding (yearly; %)			
INR < 2	0.015	0.007 to 0.030‡	Oake et al. (2008)[24]
INR within range	0.014	0.009 to 0.023‡	Oake et al. (2008)[24]
INR 3.5-5.0	0.037	0.022 to 0.063‡	Oake et al. (2008)[24]
INR > 5	0.301	0.149 to 0.609‡	Oake et al. (2008)[24]
Risk of TE (yearly; %)			
INR < 2	0.081	0.043 to 0.151‡	Oake et al. (2008)[24]
INR within range	0.024	0.012 to 0.049‡	Oake et al. (2008)[24]
INR 3.5-5.0	0.027	0.012 to 0.062‡	Oake et al. (2008)[24]
INR > 5	0.073	0.039 to 0.136‡	Oake et al. (2008)[24]
Bleeding outcomes (if bleeding occurs; %)			
ICH	0.16	0.13 to 0.19‡	FNT[101]
Fatal ICH	0.44	0.35 to 0.53‡	FNT[101]
Sequelae after ICH	0.50	0.44 to 0.56‡	Fang et al. (2007)[22]
Death/month after sequelae	0.056	0.04 to 0.07	Meckley et al. (2010)[20]
GI	0.84	§	Fang et al. (2007)[22]

TE outcomes (if TE occurs; %)			
Stroke	0.60	0.48 to 0.72‡	Assumption
Fatal stroke	0.11	0.09 to 0.13‡	FNT [101]
Sequelae after stroke	0.47	0.38 to 0.56‡	Meckley et al. (2010) [20]
Death/month after stroke	0.056	0.04 to 0.07	Meckley et al. (2010) [20]
TIA	0.40	§	Assumption
INR measurements (n)			
First month	6	4 to 8	Assumption
Consecutive months, per month	1.7	1.2 to 2.2	FNT [101]
Extra measurement after event	1	0 to 2	Assumption
Effect (%)			
Change in time within range	+12.6	+6.3 to +18.9¶	CoumaGen-II [16]
Change in time with INR <2	-9#	-4.5 to -13.5¶	CoumaGen-II [16]
Change in time with INR 3-5	-2.7#	-1.4 to -4.1¶	CoumaGen-II [16]
Change in time with INR >5	-0.9#	-0.5 to -1.4¶	CoumaGen-II [16]
Discount rate effects	1.5	0 to 3	CVZ

†95% CI. ‡±20%. §The remainder add up to 100%. ¶±50%. #Assumption based on CoumaGen-II. CVZ: Dutch Health Care Insurance Board; FNT: Federation Dutch Anticoagulation Clinics; GI: Gastrointestinal; ICH: Intracranial haemorrhage; INR: International Normalised Ratio; TE: Thromboembolic event; TIA: Transient ischaemic attack

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Table 2. Utility and cost parameters used in the model

Parameter	Base case	Range	Source
Utilities			
Atrial fibrillation	0.81	0.7784 to 0.8430	Meckley *et al.* (2010) [20]
Phenprocoumon use	-0.013	-0.005 to -0.021	Meckley *et al.* (2010) [20]
GI bleed	-0.06	-0.02 to -0.10	Meckley *et al.* (2010) [20]
ICH	-0.1385	-0.1182 to -0.1600	Meckley *et al.* (2010) [20]
TIA	-0.1032	-0.0881 to -0.1189	Meckley *et al.* (2010) [20]
Stroke	-0.1385	-0.1182 to -0.1600	Meckley *et al.* (2010) [20]
Sequelae	-0.374	-0.160 to -0.588	Meckley *et al.* (2010) [20]
Costs (€)			
Genotyping	40	20 to 160†	Howard *et al.* (2011) [25]
Phenprocoumon tablets per month	1.72	1.38 to 2.10‡	Medicijnkosten.nl [103]
INR measurement + visit to anticoagulant clinic	11.74	9 to 14‡	Schalekamp *et al.* (2006) [21]
GI bleed	12,093	9670 to 14,510‡	Schalekamp *et al.* (2006) [21]
ICH	19,132	15,300 to 22,960‡	Schalekamp *et al.* (2006) [21]
TIA	1305	1044 to 1566‡	DRGs [104]
Stroke	10,000	8000 to 12,000‡	Struijs *et al* (2006) [26]
Sequelae - first month	9000	7200 to 10,800‡	Verhoef *et al.* (2012) [27]
Sequalae - subsequent months	450	360 to 540‡	Verhoef *et al.* (2012) [27]
Discount rate costs (%)	4	0%to 8	CVZ

†Half the estimated price of a point of care test compared to the current price in a Dutch laboratory. ‡±20%. CVZ: Dutch Health Care Insurance Board; DRG: Diagnosis-related group; GI: Gastrointestinal; ICH: Intracranial haemorrhage; INR: International Normalised Ratio; TIA: Transient ischaemic attack.

would be attributable to patients at high risk for overanticoagulation who also have an increased risk of thromboembolic events, such as patients with thrombophilic syndromes.

The effects of pharmacogenetic-guided dosing were projected with the surrogate end point of percentage time spent in the different INR ranges. Meckley *et al.* [20] used data from the COUMAGEN trial [13] to model the effect of genotyping. This enabled them to obtain patient-level data on INR time within, below and above the therapeutic range. In a more recent study of Anderson *et al.*, the CoumaGen-II trial [16], data of 504 patients on a pharmacogenetic-guided warfarin dosing regimen were compared with data of parallel controls on standard warfarin dosing. In this CoumaGen-II trial, patients in the pharmacogenetic guidance group spent 10.5% more time within therapeutic INR range than the control patients in the first month (68.9 vs. 58.4%, respectively) and 12.6% more in the first 3-month period (71.2 vs. 58.6%, respectively). Patients on a genetic-guided dose had 10.3% fewer out-of-range INRs in the first month, if

compared with control patients (31.2 vs. 41.5%, respectively) and 12% fewer up to the end of the third month (30.3 vs. 42.3%, respectively). This difference was mainly driven by a reduction in subtherapeutic INRs. In our model, we used these data to calculate the percentage time in the different INR ranges in the PGx arm. We assumed that genotyping would lead to a 12.6% increase in time within range in the first month and that approximately three-quarters of this change (9%) would be attributed to a decrease in time below range. This assumption was made because in the CoumaGen-II trial INR values <1.5 were reduced by genotyping, while there was no significant difference in INR values >4 [16]. The remaining a quarter was assumed to be attributed to a decrease in time above range; 2.7% decrease in time between 3.5 and 5 and 0.9% decrease in time above 5. This effect of genotyping in the first month of therapy was linearly interpolated to zero in the sixth month. Effects were discounted at an annual rate of 1.5% in accordance with Dutch guidelines for pharmacoeconomic analyses [102].

Utilities, disutilities & cost data

In our model, we used the same estimates for quality of life (utilities) used by Meckley et al. [20]. We assumed that the disutility of using phenprocoumon therapy is the same as for using warfarin. Because the hypothetical cohort of patients included in this model all had atrial fibrillation, the utility of atrial fibrillation (0.81) was applied to all patients and a disutility of 0.013 for phenprocoumon use was applied. Disutilities were also ascribed in case of an adverse event.

Costs were determined from a healthcare sector perspective for the year 2011 in Euros (€) and discounted at 4% per year in accordance with Dutch guidelines. While these guidelines recommend using a societal perspective, we used a healthcare sector perspective since most of the cost differences were expected to be found in this sector. The costs of a point of care genotyping test were estimated to be less than US$50 per test with an instrument of approximately US$15,000 [25] and the base-case estimate for the costs of genotyping was €40. In The Netherlands, the INR is monitored on average 20.3-times per year [101]. We therefore calculated a frequency of 1.7 measurements per month, until death or an adverse event and assumed that six measurements would take place in the first month. Patients who experienced an adverse event were assumed to have an additional INR measurement that month. If patients recovered and continued using phenprocoumon, they were assumed to have one INR measurement a month until another adverse event or death. Costs of an individual anticoagulation visit including an INR measurement were derived from Schalekamp et al., who performed a previous Dutch cost–effectiveness analysis of genotyping versus standard care in acenocoumarol [21].

Assuming an average dose of one tablet per day, the costs of phenprocoumon tablets were estimated at €1.72 per month [103]. Costs of GI bleeds and ICH were derived from Schalekamp et al. [21] and stroke costs from Struijs et al. [26]. Dutch diagnosis-related groups from three different hospitals were used to estimate

the costs of a TIA [104]. Since the total costs the first year after stroke were estimated at €24,500 and the costs of subsequent years at €5500, we assumed that sequelae would cost €9000 once and €450 per month after a stroke or ICH [27]. All costs were expressed in € for the year 2011 and corrected for inflation whenever necessary.

Analyses

Base-case estimates of the costs and QALYs of the PGx strategy and standard care were determined followed by one-way sensitivity analyses to evaluate the impact of the values of different input parameters on the results. The parameters were varied over their 95% CIs or decreased and increased by 20% if a confidence interval was not available. The effect of genotyping (as found in CoumaGen-II) was decreased and increased by 50%. The costs of genotyping were varied from €20 (i.e., half the estimated price of a point of care test) to €160 (the current price of genotyping for *CYP2C9* and *VKORC1* in a Dutch laboratory) and the discount rate was varied from 0 to 3% for effects and from 0 to 8% for costs.

We also conducted the following scenario analyses:

- A best-case scenario where the costs of genotyping are €20 and the effect of genotyping is 50% larger than in the base-case analysis;
- A worst-case scenario where the costs of genotyping are €160 and the effect of genotyping is 50% smaller than in the base case analysis;
- The impact of genotype-guided dosing on INR control lasts only 1 month after treatment initiation;

- The impact of genotype-guided dosing on INR control lasts up to 1 year after treatment initiation;

The effectiveness of a pharmacogenetic-guided dosing regimen is based on the COUMAGEN trial, as in the study of Meckley *et al.* In the study of Meckley *et al.* the effectiveness is defined separately for *VKORC1/ CYP2C9* wild-type patients, *VKORC1* variant carriers/ *CYP2C9* wild-type patients and *CYP2C9* variant carriers. The last group, *CYP2C9* variant carriers, was not stratified by *VKORC1* genotype. We also modelled the effectiveness of genotyping for these three groups, but in contrast with Meckley *et al.* we applied different risks of adverse events for INR 3.5–5 and INR >5 instead of one risk of INR >3.

A probabilistic sensitivity analysis using 10,000 Monte Carlo simulations was performed to examine the combined impact of uncertainties about the values of multiple input parameters on the estimated cost–effectiveness of genotyping. This also enabled us to calculate the chance that genotyping would be cost effective at a certain threshold or willingness-to-pay. Dirichlet distributions were used for the probabilities with more than two possible results (e.g., genotype, outcome of adverse events). β distributions were used for all other probabilities and utilities, and γ distributions for the costs. The costs of genotyping were varied using a triangular distribution. All parameters were varied in this probabilistic sensitivity analysis.

RESULTS

Base case

Figure 4 shows the cumulative risk of haemorrhage and thromboembolism during the first year for the PGx strategy and for standard care. The difference between the two strategies increases during the first months, but is stable afterwards.

Table 3 shows the results of the cost–effectiveness analyses for all patients and per genotype group. Compared with standard care, the pharmacogenetic-guided dosing strategy increased the QALYs very slightly, by 0.0057 (2 days in full health), and increased costs by €15.15. The incremental cost–effectiveness ratio
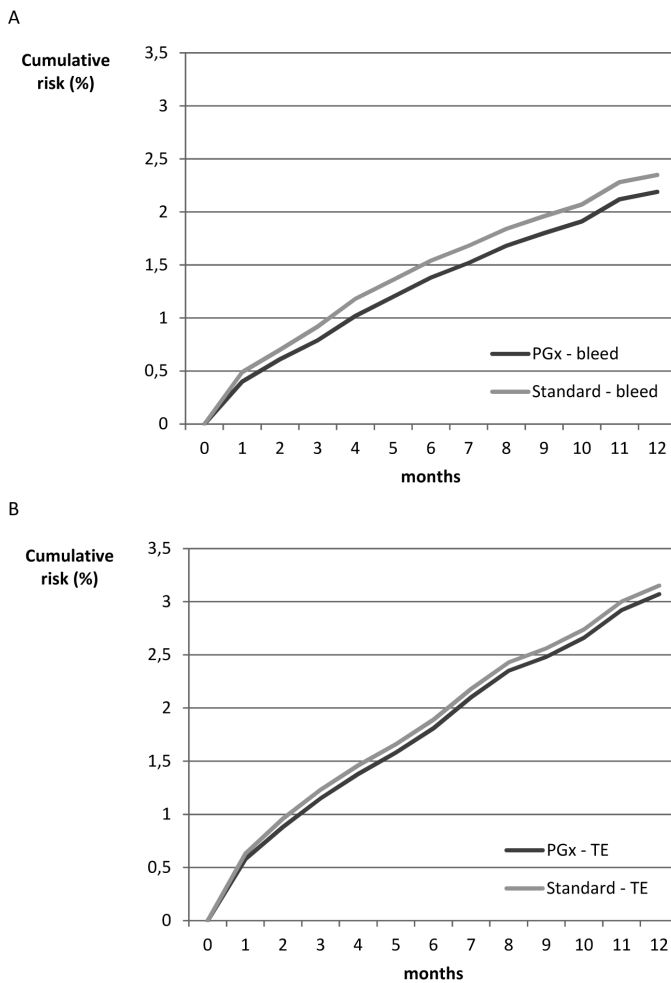
Figure 4. Cumulative risk of adverse events in the first 12 months of treatment. (**A**) Bleeding event; (**B**) thromboembolism. PGx: Pharmacogenetic-guided dosing; TE: Thromboembolic event.

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

Strategy	First year incidence per 100 patients, n (95% CI)			Total (95% CI)		ICER (€/QALY gained)
	Bleeds	TEs	Deaths	QALYs	Costs (€)	
PGx	2.19 (1.90-2.48)	3.07 (2.74-3.40)	2.57 (2.14-3.00)	9.1823 (9.11-9.25)	7949.16 (7885-8014)	
Standard	2.35 (2.06-2.64)	3.15 (2.80-3.50)	2.59 (2.16-3.02)	9.1766 (9.10-9.25)	7934.01 (7870-7998)	
Δ	-0.16 (-0.75-0.43)	-0.08 (-0.77-0.61)	-0.02 (-0.88-0.84)	0.0057 (-0.14-0.15)	15.15 (-113-144)	2658

ICER: Incremental cost–effectiveness ratio; PGx: Pharmacogenetic-guided dosing; QALY: Quality-adjusted life-year; TE: Thromboembolic event.

(ICER) was €2658 per QALY gained. Life expectancy in the pharmacogenetic-guided arm was 11.592 years versus 11.585 years in the standard care arm (difference of 0.007 years or 2.5 days). The costs per life-years saved were therefore €2225. For patients on pharmacogenetic-guided phenprocoumon therapy, the incidence of bleeds in the first year was estimated to be 0.16% lower than for patients on standard phenprocoumon treatment. The incidence of thromboembolic events was 0.08% lower and the number of deaths was 0.02% lower.

Sensitivity analysis

Figure 5 shows a tornado diagram, summarizing the results of the one-way sensitivity analysis of the 10 parameters with the largest influence on the cost–effectiveness ratio. The cost of genotyping had the largest influence on the cost–effectiveness ratio. The ICER varied from -€850 (less costly and more effective) to €23,850 when the costs of genotyping were varied from €20 to €160, respectively.

The scenario analyses confirmed that changing some key assumptions of the model had a large influence on the ICER (Table 4). In the best-case scenario, genotyping was more effective and less costly than standard care. In the worst-case scenario, however, the costs per QALY gained increased to almost €53,000. The duration of the effect of genotyping, as well as the source of effectiveness data (COUMAGEN or CoumaGen-II), also had a large impact on the cost–effectiveness.

In the probabilistic sensitivity analysis, pharmacogenetic-guided dosing was more effective and more costly in 95% of the simulations (Figure 6) and was the dominant strategy (less costly, more effective) in 4.7%. These analyses also showed that there is a 75.6% chance that genotyping is cost effective at a willingness to pay threshold of €20,000 per QALY gained (Figure 7). Figure 7 also shows the probability that genotyping would be cost effective over a range of likely thresholds.
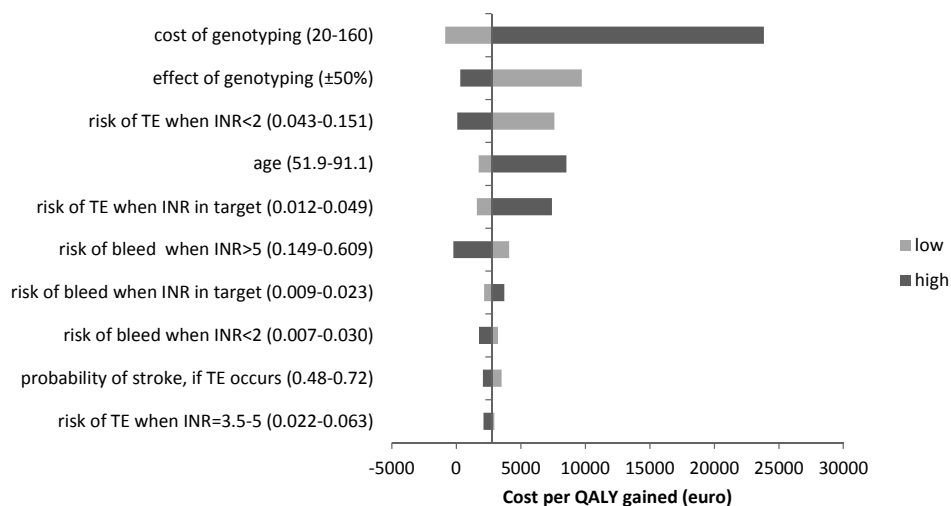
Figure 5. Tornado diagram showing the ten parameters with the largest influence on the cost–effectiveness ratio of pharmacogenetic-guided dosing versus standard care. The range of the incremental cost–effectiveness ratio in the one-way sensitivity analysis over the range of the parameter (in parentheses) is represented by the horizontal bars. A wide bar indicates that this parameter introduces a large degree of uncertainty. INR: International Normalised Ratio; TE: Thromboembolic event; QALY: Quality-adjusted life-year.

Table 4. Results of the scenario analyses

Scenario	QALY	Cost (€)	ICER (€/QALY gained)
Base case	0.0057	15.15	2658
Best case, cost of genotyping €20/ 50% more effective	0.0085	-17.29	PGx dominates
Worst case, cost of genotyping €160/ 50% less effective	0.0028	147.58	52,707
Impact of genotype-guided dosing on INR control lasts 1 month	0.0019	31.64	16,652
Impact of genotype-guided dosing on INR control lasts 1 year	0.0112	-9.20	PGx dominates
Effectiveness of genotype-guided dosing from COUMAGEN (as in Meckley *et al.* (20))	0.0014	25.54	18,242

ICER: Incremental cost–effectiveness ratio; PGx: Pharmacogenetic-guided dosing; QALY: Quality- adjusted life-year.

DISCUSSION

Our results show that pharmacogenetic-guided dosing of phenprocoumon has the potential to decrease the risk of bleeding and thromboembolic events and thereby increase health slightly. More importantly, genotyping may be able to achieve this in a cost-effective way. Based on the base-case analysis, genotyping costs approximately €2700 per QALY gained. There is, however, large uncertainty regarding some important assumptions in the model, specifically the effectiveness of a pharmacogenetic-
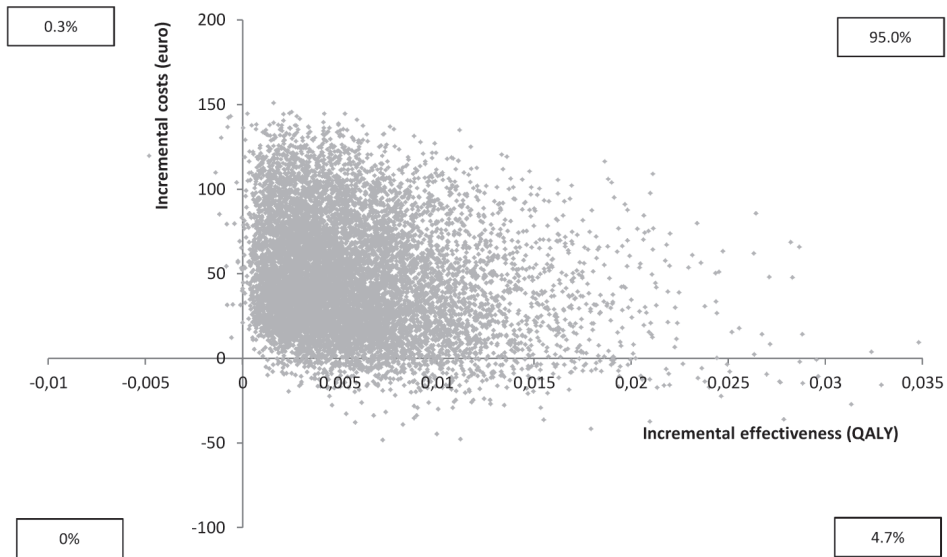
Figure 6. Scatter plot reflecting the uncertainty in the differences in costs and effectiveness between genotyping and standard care (based on probabilistic sensitivity analysis). QALY: Quality-adjusted life-year.

guided dosing regimen and the costs of the genetic test. Our model was based on existing work developed earlier to investigate the cost–effectiveness of warfarin pharmacogenomics testing [20]. Some changes were necessary to adapt it to the Dutch setting of anticoagulation clinics.

Schalekamp *et al.* studied the cost–effectiveness of *CYP2C9* genotyping in acenocoumarol users in The Netherlands and estimated the costs at €4233 per bleeding event avoided in 2006 [21]. In the current study, we not only looked at the potential decrease in the bleeding rate amongst genotyped patients, but also at the rate of thromboembolic events. If both the risk of bleeding and thromboembolic events could be decreased, this would lead to a more favourable cost–effectiveness ratio for genotype- guided dosing. Another addition in our model compared

with Schalekamp and coworkers is that we also looked at *VKORC1* genotype instead of only at *CYP2C9* genotype. Lastly, we performed a cost–utility analyses (i.e., costs per QALY gained) while Schalekamp *et al.* looked at cost per bleeding event avoided. Decision makers often require a cost–utility analysis. Since the Dutch guidelines do not express a threshold or willingness to pay, we examined cost–effectiveness of genotyping at various thresholds and used a threshold of €20,000 in the analysis because of its use in previous reimbursement decisions [32].

In a cost–effectiveness study on warfarin pharmacogenetics by Patrick *et al.* it was shown that age had the largest effect on the ICER in the one-way sensitivity analysis [29]. In our study, a large effect of age was also seen, but the largest effect was seen for the costs of genotyping. This also
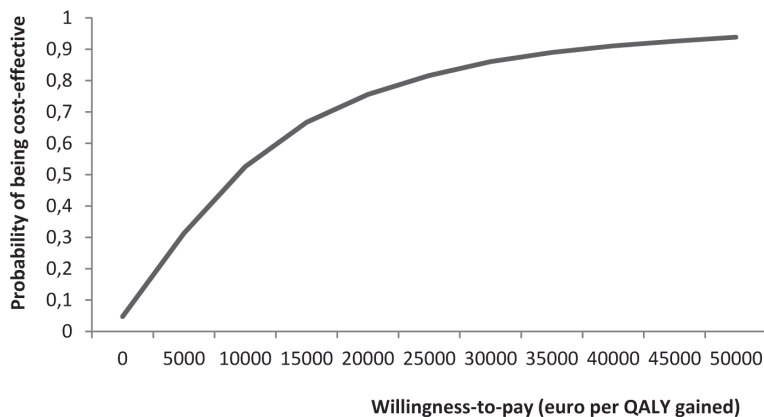
Figure 7. Cost–effectiveness acceptability curve. This curve, generated from the Monte Carlo simulations, represents the probability that pharmacogenetic-guided dosing would be cost effective compared with standard care at different thresholds of willingness-to-pay. QALY: Quality-adjusted life-year.

had a large effect in the study of Patrick *et al.,* although this effect was smaller than the effect of age. These differences cannot simply be explained by differences in the ranges in age and genotype costs that were studied and may likely be due to differences in how age was linked to health outcomes. In two other cost–effectiveness studies on warfarin pharmacogenetics, by You *et al.* and by Eckman *et al.,* cost of genotyping also played a very large role in the variation of ICER in one-way sensitivity analysis [30,31].

This study is also the first cost–effectiveness study on coumarin pharmacogenetics using an existing model. Partly owing to the differences in model characteristics, results of previous analyses were difficult to compare. In this study we adapted the previously published model of Meckley *et al.* [20]. The estimated ICER in the study of Meckley *et al.* was considerably higher than in our study (US$60,750), which indicates that genotyping might have a bigger chance of being cost effective

in The Netherlands than in the USA. This difference is probably mainly due to the higher costs of genotyping (US$175) in the USA, but is also related to the smaller effect estimate used in the study of Meckley *et al.* The effect estimate in the study of Meckley *et al.* was derived from the first COUMAGEN [13] trial instead of the more recent CoumaGen-II trial [16] used in our study. Genotyping had a smaller effect in the first trial than in the more recent trial. We have used data from the CoumaGen-II trial, as this was the most recent data and the largest trial performed at this moment.

A major limitation of our study is the lack of reliable data on the effectiveness of genotyping phenprocoumon patients from appropriately powered clinical trials. Some large ongoing clinical trials are investigating the impact of genotyping warfarin patients [18,19]. In the EU- PACT trial, phenprocoumon and acenocoumarol are also being investigated [17]. The results of these trials can be used to investigate

the cost–effectiveness further. Another uncertainty in the model is the cost of a genotyping test. It is estimated a novel point of care test would cost less than US$50 to genotype a patient for *CYP2C9* and *VKORC1*, but the price will also depend on how often this test will be used [25]. If pharmacogenetic testing becomes standard practice in treatment with phenprocoumon (or warfarin or acenocoumarol) the price of the test will probably decrease.

Another possible limitation of this study is the use of a surrogate end point (INR) to estimate the effectiveness of genotyping instead of using the risk of bleeding and thrombosis directly. However, time in INR range is the primary outcome in two of the large trials [17,18], and this model could therefore also be used when these data become available. We did not use outcomes as acute coronary syndrome or angina pectoris or invasive interventions such as coronary bypass surgery or percutaneous coronary interventions. The consequence of this is not clear. To our knowledge, there is no data on whether genotype-guided dosing will change the risk on the occurrence of these events.

It is possible that some parameters that are varied in the probabilistic sensitivity analysis are correlated (e.g., age and bleeding risk). However, we did not include multivariate distributions, because this data was not available. We therefore assumed independence of these variables, which could have inflated the second order uncertainty.

A strength of this study is the fact that we were able to use an existing model and adapt it to the desired setting and improve it to reflect the clinical situation more precisely, which makes it easier to compare the different studies.

CONCLUSION

Compared with standard care, pharmacogenetic-guided dosing has the potential to increase health and may be able to achieve this in a cost-effective way. It is, however, too early to conclude whether or not patients starting phenprocoumon should be genotyped, because of significant uncertainties regarding some important assumptions in the model. The main factors for this uncertainty are the effectiveness of a pharmacogenetic-guided dosing regimen and the costs of the genetic test.

FUTURE PERSPECTIVE

Recently, new oral anticoagulants (direct thrombin inhibitors and factor Xa inhibitors) have been developed for stroke prevention in patients with atrial fibrillation and these are thought be good alternatives for coumarin derivatives [33,34]. These drugs have some advantages over coumarin anticoagulants, such as not requiring frequent monitoring (which is often considered burdensome for the patient). On the other hand, no appropriate antidote is available yet and bleedings tend to be more serious. Moreover, these new drugs are more expensive than coumarin derivatives, so it is also important to study their cost–effectiveness [35,36]. In the RE-LY trial the investigators found that the

benefit of dabigatran compared with warfarin was related to the quality of care of the warfarin treatment [37]. An important question to be answered in the coming years is whether it would be better to improve the current standard therapy with coumarin derivatives by use of pharmacogenetics or to use an entirely new drug. Both the effectiveness and the cost–effectiveness of these options should be investigated. Possibly, both options (the new oral anticoagulants and pharmacogenetic-guided dosing of coumarin anticoagulants) could be used in the future. In some situations, the costs will play a more important role and decision-makers will try to find a cost-saving solution. In countries where the quality of coumarin treatment is currently low, genotyping could possibly be a cost-saving option.

Currently, several large trials are investigating the clinical effectiveness of genotype-guided dosing of coumarin derivatives [17-19]. When more information on this subject becomes available in the coming years, the model used in this study could be adapted and used to assess the cost–effectiveness of pharmacogenetics using phenprocoumon, acenocoumarol or warfarin to treat patients with atrial fibrillation versus standard care. A value of information analysis can be performed to determine whether or not it is worthwhile to collect extra information to reduce uncertainty about the cost–effectiveness of a new treatment. As new information about the effectiveness of genotyping is expected in the very near future, we did not think it useful to perform such a value of information analysis at this time. However, it would be worthwhile to perform such an analysis after all information from the trials has been analysed.

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COST–EFFECTIVENESS OF PHARMACOGENETICS IN ANTICOAGULATION: INTERNATIONAL DIFFERENCES IN HEALTHCARE SYSTEMS AND COSTS

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ABSTRACT

Genotyping patients for *CYP2C9* and *VKORC1* polymorphisms can improve the accuracy of dosing during the initiation of anticoagulation with vitamin K antagonists (coumarin derivatives). The anticipated degree of improvement in the safety of anticoagulation with coumarin derivatives through genotyping may vary depending on the quality of patient care, which varies both with and among countries. The management and the cost of anticoagulant care can therefore influence the cost–effectiveness of genotyping within any given country. In this article, we provide an overview of the cost–effectiveness of pharmacogenetics-guided dosing of coumarin derivatives. We describe the organization of anticoagulant care in the UK, Sweden, The Netherlands, Greece, Germany and Austria, where a genotype-guided dosing algorithm is currently being investigated as part of the EU-PACT trial. We also explore the costs of anticoagulant care for the treatment of atrial fibrillation in these countries.

INTRODUCTION

Coumarin derivatives are commonly prescribed for the treatment and prevention of thromboembolic events [1]. Anticoagulation therapy with coumarin derivatives requires frequent monitoring of the International Normalised Ratio (INR), an indicator of the clotting tendency of blood, to maintain within a narrow therapeutic range. For patients with atrial fibrillation, the INR target range is normally 2.0–3.0, with some exceptions such as 2.5–3.5 in The Netherlands [2]. Wide inter- and intra-patient variability in dose requirement exists, which makes it difficult to predict the right dose. INR values below the therapeutic range lead to loss of efficacy and an increased risk of thromboembolic events, while INR values above the therapeutic range lead to toxicity with an increased risk of bleeding events. The latter can be minor or major and life-threatening or fatal, such as intracranial haemorrhage (ICH) [3]. The variation in dose requirements can be explained by several factors, including age, weight, height, vitamin K intake and concomitant medication; however, genetic factors also explain a substantial proportion of this variability [4]. Genotyping the *CYP2C9* and *VKORC1* genes may help to predict the required coumarin dose prior to treatment of the patients [5]. *CYP2C9* encodes the main metabolizing enzyme of coumarin anticoagulants, CYP2C9, and *VKORC1* encodes the pharmacodynamic target enzyme for coumarin anticoagulants, VKORC1. By prescribing a dose that is based on genotype and clinical factors, it is anticipated that patients will both reach a therapeutic INR quicker and maintain within range for longer. This could decrease the risk of adverse events, including stroke and bleeding; however, supporting evidence from appropriately powered clinical trials are hitherto unavailable.

For the implementation of pharmacogenetic testing in practice, further evidence of the clinical effectiveness and cost–effectiveness is necessary. Currently, two major clinical trials are ongoing to investigate the former [6,7], and an economic

analysis is planned to estimate the incremental cost–effectiveness of the new dosing strategy compared with standard care (i.e., a nongenotype-guided dosing regimen). Several cost–effectiveness analyses of genotyping have previously been performed, but with limited conclusions about their economic value, principally because of the uncertainty in the clinical evidence [8-16]. Furthermore, most of the cost–effectiveness studies were conducted in the USA, where anticoagulation services are organised differently from European countries. However, even among European countries, different models of care apply. In some countries, treatment is managed by specialised physicians in anticoagulation clinics, while in others, this is being performed by hospital specialists (including anticoagulation pharmacists or nurses) or by the general practitioners (GPs). These

differences contribute to variation in the quality [17-21] and costs of care, and will impact on the cost–effectiveness of genotyping.

The aim of this article is to describe the current standards of coumarin anticoagulant therapy and its associated costs, relating to the management of atrial fibrillation in different European countries. First, we provide a brief overview of the results of the cost–effectiveness analyses of pharmacogenetic-guided dosing of coumarin derivatives performed to date. Next, we describe the organization of anticoagulant care in the UK, Sweden, The Netherlands, Greece, Germany and Austria; countries in which a genotype-guided dosing algorithm is currently being investigated as part of the EU-PACT trial. Finally, we summarise the costs of anticoagulant therapy for each country.

METHOD

We reviewed the literature for economic evaluations of pharmacogenetic testing in relation to anticoagulation with coumarin derivatives. Relevant articles were sourced from our previous related review [22], and from an electronic search of PubMed, following the same search strategy. In our previous review, nine articles were selected. More details about this selection and the quality assessment can be found elsewhere [22]. During our PubMed search, we found one additional article describing the cost–effectiveness of genotype-guided warfarin dosing [16]. We also conducted literature searches for details of current anticoagulant care systems in the sample countries, as well as the associated costs.

Additional information, sourced from governmental organizations or from interviews with experts, supplemented our reviews.

We examined the following characteristics of each system: the setting of anticoagulant care (i.e., hospital, GP or specialised clinic), most frequently used coumarin derivative, population, mean annual frequency of INR monitoring, mean percentage time in therapeutic INR range, major bleeding rate, stroke rate and the number of self-managing patients. We also collected information about costs of the coumarin anticoagulant and INR measurements, and that of managing a gastrointestinal (GI) bleed, ICH, stroke and transient ischaemic attack (TIA).

Overview of available cost–effectiveness analyses

CYP2C9 genotyping

In 2003, Higashi and Veenstra made an approximation of the cost–effectiveness of genotyping warfarin users for *CYP2C9* in the USA to illustrate the concepts of cost–effectiveness analyses of pharmacogenetic testing [8]. In their study the authors estimated the costs of a genotype-guided dosing strategy to be US$5940 per bleeding event avoided. Because this analysis was only used for didactic purposes, it was incomplete and a comparator was not mentioned. However, 1 year later You *et al.* performed the first full economic evaluation, which resulted in a cost–effectiveness ratio of US$5778 per bleeding averted, compared with standard care [9]. The comparator in all following studies was standard anticoagulation care. McWilliam *et al.* estimated the cost per bleeding averted at US$13,500 in 2008 [11]. Schalekamp *et al.* reported the first (and only) cost–effectiveness analysis focused on the use of acenocoumarol in The Netherlands instead of the use of warfarin in the US in 2006 [15]. The authors found that the cost per bleeding event avoided was US$5151. This cost–effectiveness ratio was sensitive to different parameters, including the bleeding rate, prevalence of a *CYP2C9* polymorphism and the cost of genotyping.

CYP2C9 & VKORC1 genotyping

Some cost–effectiveness analyses have also included genotyping for *VKORC1* [10,12-14], which was first reported to have an effect on the required coumarin dose in 2005 [23]. These studies also include a measure of utility and were therefore able to present their estimates of cost–effectiveness as cost per quality-adjusted life-year (QALY) gained, which ranged from US$171,000–347,000. The willingness to pay in the USA is US$50,000–100,000 per QALY gained [24].

One important limitation of the studies performed before 2010 is that the effectiveness of genotyping was based mainly on assumptions and not on robust, appropriately powered, clinical trial evidence. Meckley *et al.* used time below, within and above therapeutic INR range as a surrogate to estimate and compare the risk of different adverse events in both the genotyped group and the standard care group [16]. They concluded that genotyping was more effective than standard care, but at a cost of US$60,750 per QALY gained. The authors also performed a probabilistic sensitivity analysis and showed that the chance that genotyping would be cost-effective at a threshold of US$50,000 per QALY gained was 46%.

The results of the different cost–effectiveness studies published in the past vary widely. The primary cause of this variation relates to the uncertainty around the effectiveness of genotyping. This uncertainty is caused by the small number of randomised controlled trials, and the heterogeneity of patient populations, trial design, definitions of outcomes and reporting of results among these randomised controlled trials. Another factor is the estimation of costs; for example, the cost of genotyping varied from US$67–575. However, since the costs of a pharmacogenetic test are steadily decreasing, there is a greater likelihood that genotyping will be cost-effective provided that it leads to marginal health benefits compared with standard care.

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Differences among studies may also be explained by the wide range in the scope of the analysis (e.g., productivity costs and time horizon), which can, for example, influence the estimated overall costs of major bleeding and stroke.

Management of anticoagulant treatment in different countries

Anticoagulant treatment is organised differently among different countries. In this section, we describe the main characteristics of the organization of treatment with coumarin derivatives in selected European countries. The principal findings are summarised in Table 1.

UK

Approximately 950,000 patients are using warfarin in the UK (prevalence is approximately 1.6%) [17,25]. Anticoagulation therapy services are delivered in a number of different settings including full-service provision in secondary or primary care, shared provision between primary and secondary care and domiciliary provision. An estimated 20,000 (2%) patients self-monitor their INR [Heneghan C, Pers. Comm.]. Most patients are initiated on warfarin in hospital and managed long term by GPs [17,101]. The frequency of INR measurements is usually between eight and 12 per year [26]. However, there is considerable variation in published reports. In a study by Jones *et al.*, the mean time between consecutive INR measurements was 15.7 days, implying an average of 23 INR measurements per year [27]; and Jorgensen *et al.* reported a median of 16 (range 1–57) INR measurements over a 6-month period [28]. The percentage time spent within therapeutic INR range in routine UK practice is, on average, 63.1% [29].

This compares with estimates of 60–68% from other studies of routine care [27,30,31], and 72% in the UK centres that recruited patients for the RE-LY trial [21].

Based on a UK General Practice Research Database review of patients with atrial fibrillation, Rietbrock *et al.* determined an ischaemic stroke rate of 3.2 events per 100 patient-years [32]. The risk of major bleeds was estimated by NICE at 2.4% per year in its costing report on atrial fibrillation [102]. This was based on the study by Fitzmaurice *et al.*, which suggested that the annual rate is 2.4–8.1% [33], Abdelhafiz and Wheeldon who calculated a rate of 2% [34] and Carroll and Majeed who suggested a rate of 2.3% per year [35].

Sweden

In Sweden approximately 150,000 patients are using warfarin (prevalence is approximately 1.6%) [36,37]. The treatment is managed by anticoagulation centres in a hospital setting or in primary care [37]. The proportion of patients monitored in primary healthcare units is dependent on local tradition and differs from region to region. A large difference between regions can be seen in the study of Wallvik *et al.*, where the proportion of warfarin users monitored by the GP ranged from only 10% up to 80% [38]. In Stockholm most patients are treated by the GP [39]. In many primary healthcare clinics the GP works alone, but often their GP is also assisted by a nurse. The patient can either come to the clinic for INR measurement or a blood sample for INR measurement can be taken at the patient's home [40]. In the study of Wieloch *et al.*, the INR is measured on average 13.6-times per year [37]. This

is in line with the frequency of INR measurements in the study of Davidson *et al.* for patients treated in primary care (13.7) [41]. In a hospital clinic, the INR was measured 16.9-times per year. In the first year, five extra measurements were assumed. Björholt *et al.* showed that when patients were initiated on warfarin, the INR was measured 12.4-times in the first 3 months and 17.1-times in months 4–12 [42]. In this study, the frequency of INR measurements in the second year was 16.2. The average percentage time spent within the target INR range was found to be 76.2% and this percentage was somewhat higher in primary care centres (80.3%) than in hospital-based centres (75.7%) [37]. The exact number of patients on self-management is unknown, as well as the percentage time in range for this treatment strategy. The number of self-testing patients has been estimated at 1500 Svensson P, Pers. Comm..

Lind *et al.* calculated an incidence of a bleeding event of 3.3 per 100 patient-years [43]. In an earlier study by these authors, the incidence of a GI bleed and an ICH was 1.3 and 0.6 per 100 patient-years, respectively [44]. Similar rates were observed in the study of Asberg *et al.* (GI bleed: 1.18 per 100 patient-years; ICH: 0.89 per 100 patient-years) [45], Friberg *et al.* (ICH: 0.6 per 100 patient-years) [46] and Wallvik *et al.* (GI bleed: 1.4 per 100 patient-years; ICH: 0.7 per 100 patient-years) [38]. Lind *et al.* also studied the occurrence of stroke and showed a rate of 2.8 strokes per 100 patient-years [43]. In a study by Åsberg *et al.*, ischaemic stroke occurred 3.5-times per 100 patient-years in patients who were treated with warfarin after a first stroke [47].

The Netherlands

In The Netherlands, 398,000 patients were treated with a coumarin derivative in 2010 (prevalence is approximately 2.4%) [103]. The most frequently used coumarin anticoagulant is acenocoumarol (81%), while the remaining patients are given phenprocoumon [103]. All coumarin users are referred to a specialised anticoagulation clinic to monitor their treatment. Patients either go to the clinic for INR measurement (60%) or are visited at home (40%) by a nurse from the clinic. The anticoagulant dose and interval between monitoring visits is determined by specialised physicians [2,48,103]. The target INR in The Netherlands is higher than in other European countries. The target range for atrial fibrillation for example, is 2.5–3.5 [49]. The median frequency of INR measurements per patient per year was 20.3 in 2010 and the median percentage time in target INR range was 78.5% for patients on long-term acenocoumarol or phenprocoumon treatment (6 months to lifelong). For patients on short-term treatment (2–6 months) with acenocoumarol or phenprocoumon or in the initiation phase (0–2 months), this percentage was 74.3 and 62.6%, respectively [103]. Torn et al. demonstrated that the percentage time in range between different age groups varies from 61% in patients older than 80 years to 68% in patients aged between 60 and 70 years [50]. In a study of Gadisseur et al. the percentage time in range for patients treated in a specialised anticoagulation clinic was 63.5% [51]. This study also investigated the quality of patient self-management and found that patients on self-management

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Table 1. Summary characteristics (point estimates) of anticoagulant care in different countries

	United Kingdom	**Sweden**
Setting	GP (hospital initiates) [17,101]	GP/Hospital [37]
Most frequently used coumarin anticoagulant	Warfarin [17,25]	Warfarin [37]
Population, n (% prevalence)	950,000 (1.6) [17]	150,000 (1.6) [36]
Frequency of INR monitoring	10 [26]	13.6 [37]
Time in target INR range (%)	63.1 [29]	76.2 [37]
Annual major bleeding rate	0.024 [102]	0.033 [43]
Annual stroke rate	0.032 [32]	0.028 [43]
Frequency of self-management (%)	20,000 (2.1) [Heneghan C, Pers. Comm.]	1500 (1) [Svensson P, Pers. Comm]

GP: General practitioner; INR: International Normalised Ratio; UNK: Not known.

had a slightly higher percentage time in range (68%). According to the Federation of Dutch Thrombosis Services (FNT), 25,000 patients were self-managing in 2010, with a median percentage time in range of 80% [103]. In both the report of the FNT and the study of Gadisseur et al. the percentage time in range for phenprocoumon was higher (4–12%) than for acenocoumarol [51,103].

The FNT also keeps a record of bleeding or thromboembolic events during coumarin use. In 2010, the incidence of major bleeding was 1.4 per 100 patient-years. There were 0.2 ICHs and 0.4 GI bleeds per 100 patient-years. Ischaemic strokes occurred 0.1-times per 100 patient-years [103]. The frequency of these events was low in comparison with earlier studies by Torn et al. and Visser et al. [2,52]. In the study of Torn et al., the rate of major bleeding and thromboembolic events was 2.9 and 1.4 per 100 patient-years, respectively [2]. Visser et al. demonstrated an incidence of four major bleeding events per 100 patients-years (2.1 GI; 0.76 ICH) [52].

Greece

It is estimated that in Greece only 20,000 patients are on chronic anticoagulant therapy (prevalence is approximately 0.2%) [53]. The number of acenocoumarol users is currently probably higher than 20,000; however, no official number is available [Manolopoulos VG, Pers. Comm]). Acenocoumarol is the most frequently used coumarin anticoagulant here, followed by warfarin [54]. In Greece, healthcare is organised by either the private sector or the public sector, and it is estimated that approximately 60% of the acenocoumarol users are treated in the private healthcare sector [53]. Approximately 30% of the patients are treated in insurance funds' healthcare facilities and 10% in specialised oral anticoagulant therapy hospital clinics. On average, patients visit the physician's office once per month for INR measurement [53,55]. Geitona et al. studied the costs of anticoagulant treatment in patients monitored with the traditional method and with self-monitoring [53]. In this study, a panel estimated the probability of complications. For the traditional method, the incidence of haemorrhagic complications was 2.8%

The Netherlands	Greece	Germany	Austria
Specialised anticoagulation clinics [2,48]	Private sector [53]	GP /Hospital [Stingl J, Pers. Comm.]	GP (hospital initiates) [Haschke-Becher E, Pers. Comm.]
Acenocoumarol [103]	Acenocoumarol [54]	Phenprocoumon [57]	Phenprocoumon [Haschke-Becher E, Pers. Comm.]
398,000 (2.4) [103]	20,000 (0.2) [53]	750,000 (0.9) [56]	60,000 (0.7) [104]
20.3 [103]	12 [53,55]	14 [58]	12 [65]
78.5 [103]	UNK	56 [59]	66 [61]
0.014 [103]	0.028 [53]	0.027 (gastrointestinal bleed) [59]	UNK
0.001 [103]	0.053 [53]	0.022 [59]	UNK
25,000 (6) [103]	20 (<0.1) [53]	130,000 (17) [62]	3500 (6) [105]

and the incidence of thromboembolic episodes was 5.3%. The risk of complications was lower in specialised oral anticoagulation clinics (2.5% haemorrhagic complications and 0.9% thromboembolic episodes) and for self-monitoring (1.5% haemorrhagic complications and 0.9% thromboembolic episodes). Less than 0.1% of the acenocoumarol users perform self-monitoring [53].

Germany

Approximately 750,000 patients use a coumarin derivative in Germany (prevalence is approximately 0.9%) [56]. The majority of these patients are treated with phenprocoumon [57]. In most cases, the therapy is managed by the GP who checks the INR on average 14-times per year [Stingl J. Pers. Comm.,58]. In a study on adherence to anticoagulation guidelines in patients with atrial fibrillation, McBride *et al.* reported that patients spent 56% of the time in the therapeutic INR range [59]. Voller *et al.* studied the quality of patient self-management and found that these patients spent 67.8% of the time in the therapeutic

INR range versus 58.5% in patients who were managed by the GP [60]. In a study by Siebenhofer *et al.* self-management was compared with routine care in Germany and Austria. In the self-management group, the percentage time within target range was 73, versus 66% in the routine-care group [61]. Approximately 130,000–160,000 coumarin users are self-managing [62,63]. McBride *et al.* also investigated the complications that occurred during a 9-month observation period. During this period, 1.7% of the patients suffered a stroke, 0.3% a TIA and 19% of the patients had a bleeding event, which were mostly gum and nasal bleeds (2% were a GI bleed) [59]. Jobski *et al.* estimated an incidence of hospitalizations for bleeding of 2.79 per 100 patient-years [64]. The annual incidence of events shown in Table 1 are based on conversions of these figures to a 1-year period.

Austria

Phenprocoumon is the most frequently used coumarin anticoagulant in Austria and treatment is normally initiated in the hospital and monitoring is done by the

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GP [Haschke-Becher E, Pers. Comm.]. More than 60,000 patients are on long-term phenprocoumon treatment in Austria (prevalence is approximately 0.7%) [104]. Currently, routine care in Austria involves monthly INR monitoring [65]. Approximately 3500 patients are undertaking self-management [105]. In a study of Austria and Germany, Siebenhofer *et al.* found that the percentage time within the target INR range of 2.0–3.0 in routine care was 66 and 74% for patients doing self-management [61]. Data on percentage time within the INR target range and risks of complications such as bleeding or stroke rate were not available for Austria specifically.

Cost of anticoagulant treatment

As can be expected, the costs associated with anticoagulant treatment and complications differ among European countries. In the section that follows, we describe the main cost parameters associated with coumarin use in the sample countries. The costs of the coumarin anticoagulant, INR measurements and management of major bleedings (i.e., GI bleeds and ICH), strokes and TIAs are summarised per country in Table 2. All costs in this table are expressed in euros for the year 2011.

UK

The total cost of anticoagulation services in England, based on more than 2.4 million episodes, was GB£51 million in 2010/11 (€63 million) – equivalent to GB£20.97 (€26.00) per unit of activity [106]. In its appraisals of newer oral anticoagulants, NICE considered a cost of GB£241.54 (€299.50) per patient per annum to be a realistic estimate for INR monitoring [107,108].

However, there is considerable variation in published estimates [109]. According to Ali *et al.* the total costs of monitoring, including INR measurement, travel, time off work, nurse visits and postage, were GB£117.60 (€145.82) per year in 2011 [66]; based on a large prospective cohort study [28], Pink *et al.* estimated an annual cost of GB£198.39 (€246 in 2011) [67]. Warfarin tablets cost approximately GB£41 (€52 in 2011) per year [67]. According to Pink *et al.* a major bleed costs GB£1685 (€2129 in 2011) to manage [67]. Jowett *et al.* calculated the costs of a GI bleed to be GB£1051 (€1303 in 2011) and an ICH GB£2059/€2746 [68]. Kansal *et al.* reported that the costs of a GI bleed were higher, at GB£1594 (€2009 in 2011); and the cost of ICH varied from GB£3059 (€3855 in 2011) to GB£24,234 (€30,537 in 2011) depending on the severity [69]. Jowett *et al.* reported that the acute costs for an ischaemic stroke vary from GB£1746 to GB£2574 (mean costs were €2880 in 2011), depending on the severity [68]. After the acute phase, the costs are estimated at GB£13.37 (€17.83 in 2011) per day. Hemingway *et al.* estimated the total costs for the first year after a stroke to be GB£9845 (€12,208 in 2011) followed by GB£2572 (€3506 in 2011) in each subsequent year [70]. Jowett *et al.* estimated the costs of a TIA at GB£756 (€1008 in 2011) [68], compared with GB£1064 (€1341 in 2011) by Kansal *et al.* [69].

Sweden

Costs of INR monitoring were estimated at €22 per measurement in Sweden [111]. In two other studies, the costs of an INR measurement were calculated for hospital clinics and primary care separately. In these

Table 2. Cost associated with anticoagulant care and complications in different countries

Cost parameter	United Kingdom	Sweden	The Netherlands	Greece	Germany	Austria
Coumarin anticoagulant, per year	€52 [67]	€66 [41]	€30.37 [113]	€25.88 [55]	€181 [77]	UNK
INR monitoring per measurement (per year)	€26 (€300) [106-108]	€22 (€300) [111]	€11.74 (€238) [15]	€22 (€264) [53]	€5.28+ (€74) [58]	UNK
Gastrointestinal bleed, acute costs	€1303 [68]	€3986 [110]	€12,093 [15,71]	€655 [115]	€2000 [58]	UNK
Intracranial haemorrhage, acute costs	€2553 [68]	€11,503 [111]	€19,132 [72]	€2050 [115]	€10,951 [78]	UNK
Stroke, acute costs	€2678 [68]	€11,503 [111]	€10,000 [74]	€2050 [115]	€3804 [77]	€5589 [82]
Stroke, costs first year	€12,208 [70]	€18,503 [111]	€24,493 [74]	€12,756 [76]	€10,551 [79]	€23,852 [81]
Transient ischaemic attack, acute costs	€937 [68]	€2561 [110]	€1305 [114]	€ 807 [115]	€2061 [77]	UNK

+ Only diagnostics. INR: International Normalised Ratio; UNK: Not known.

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studies the costs were approximately €21 if the patient was managed by a hospital clinic and €62 if managed by the GP [36,41]. Warfarin tablets have been estimated to cost approximately €66 (€67 in 2011) per patient per year [41]. Costs of a complicated GI bleed, very complicated GI bleed and uncomplicated GI bleed were €3986, €5939 and €2686, respectively, according to a comprehensive price list used for reimbursements [110]. In a Swedish study, in-hospital costs for stroke were €11,503 and total costs 1 year after stroke were €18,503 [111]. From the second year after stroke, costs were €5332 [111]. In Swedish studies the costs of stroke are often used as an estimate for the costs of an ICH [112]. The costs of a TIA were €2561 [110].

The Netherlands
Schalekamp *et al.* reported that the costs for INR measurement were on average €10.23 (€11.74 in 2011). INR measurement in the anticoagulant clinic was slightly cheaper than when the blood sample was taken at home (€11.05 vs 12.43, respectively) [15]. Acenocoumarol tablets cost on average €30.37 per year and phenprocoumon tablets cost €20.68 per year [113]. A GI bleed was estimated to cost €11,900 (€12,093 in 2011) by calculation of the weighted mean of duodenum and stomach bleeds without perforation [15,71]. Hospitalization costs for a subarachnoid haemorrhage were estimated to be €15,584 in 2001 (€19,132 in 2011) and the total costs for the first year after this bleed were estimated at €24,435 (€29,999 in 2011) [72]. These costs are comparable with the costs estimated for a bleed in the CNS including the costs for a nursing home of €28,419 in

2004 (€32,614 in 2011) [73]. According to Struijs *et al.*, hospital costs for a stroke were €7971 (€10,000 in 2011) [74]. Total costs for the first year were €19,523 (€24,493 in 2011) and the costs for every subsequent year after stroke €4427 (€5554 in 2011). The costs of a TIA in Dutch diagnosis-related groups of three different hospitals were on average €1305 in 2011 [114].

Greece
Geitona *et al.* investigated the costs of different monitoring methods for oral anticoagulation [53]. In this study private market prices as well as shadow prices were used, because of the discrepancies between nominal and actual prices in the public healthcare sector in Greece. The market price of an INR measurement was €20 (€22 in 2011) and the shadow price was €15 (€16.85 in 2011). The price of a medical visit for anticoagulation monitoring was €30 (€33 in 2011; shadow price €20–€22.50 in 2011). In a study of Daskalopoulos *et al.* in 2005, the costs of an INR measurement were €20.63 (€23.17 in 2011 [55]), which is similar to the market price used by Geitona *et al.* [53]. In the study by Daskalopoulos *et al.*, the costs of acenocoumarol tablets were €11.52 for 6 months, or €23.04 (€25.88 in 2011) per year. A GI bleed without severe comorbid medical conditions or devastating complications costs €375 and with severe comorbid medical conditions or devastating complications it costs €934 [115]. An ischaemic stroke and ICH cost between €1625 and €2475 [115]. In a study by Gioldasis *et al.*, costs of a stroke were €3215 (€3384 in 2011) and of an ICH €5305 (€5586 in 2011) [75]. Maniadakis *et*

al. estimated the costs for hospitalization for stroke to be €842 (€887 in 2011) and total costs of the first year after stroke to be €12,115 (€12,756 in 2011) [76]. A TIA costs between €495 and €1118 [115]. Table 2 shows the average price of adverse events with and without severe comorbid medical conditions or devastating complications.

Germany

In Germany, the cost of diagnostics for an INR measurement was €4.60 in 2004 (€5.28 in 2011) [58] and the cost of oral anticoagulation was €14.76 per month in 2009 (€15 in 2011) [77]. According to McBride *et al.* the cost of hospital admission for a GI bleed was €1742.50 and the cost of other bleeds were €1802.14 in 2004 (€2000 and 2068, respectively in 2011) [58]. Costs of an ICH were €8920 (€10,951 in 2011) in the study of Weimar *et al.* [78]. Total direct costs of a stroke were €9394 (€10,551 in 2011) in the study of Brüggenjürgen *et al.* [79]. These authors showed that the costs of a stroke were higher in patients with atrial fibrillation specifically (€11,799 in 2005 and €13,252 in 2011). Reinhold *et al.* showed the cost for acute hospitalization (€3804) and rehabilitation clinic (€7532) separately [77]. In this study, the costs of a TIA were €2022.50 (€2061 in 2011). Kolominsky-Rabas *et al.* estimated the yearly costs for stroke after the first year to be €5479 (€6288 in 2011) [80].

Austria

Data on costs of phenprocoumon tablets, INR monitoring and bleeding were not available for Austria specifically. Wancata *et al.* estimated that the costs of a stroke in Austria were €20,784 in 2004 (€23,852 in 2011) [81]. Acute costs for stroke were €4404 (€5589 in 2011), in a study by Levy *et al.* [82].

DISCUSSION

Anticoagulant treatment with coumarin derivatives is challenging because of the narrow therapeutic window and the associated risk of bleeding or thromboembolic events when the dose is either too high or too low. Consequently, INR is monitored frequently, as is evidenced by our analysis of six European countries. Our review also highlights the many differences in organization of anticoagulant care. The setting in which the INR monitoring and coumarin dosing takes place varies from a specialised anticoagulation clinic to the GP and hospital settings. The frequency of INR monitoring varies from 10- to 20-times per year. A marked difference in the prevalence of coumarin use among the different countries can be seen. In the UK, Sweden and The Netherlands the prevalence is approximately 2%, while in Greece, Germany and Austria the prevalence seems to be lower than 1%. A possible explanation for this could be that physicians prescribe coumarin anticoagulants less frequently in these countries, because of different guidelines or because they are hesitant to prescribe the drug due to possible bleeding complications. Unfortunately there is no literature describing this.

Another possible reason for the difference found could be that the

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reporting of coumarin use is less well organised and the true prevalence of coumarin use is actually higher than that found in the literature. The apparent large difference between 0.2 and 2.4% could also be caused by differences in methods of assessment across these studies and the year these studies were conducted.

The quality of anticoagulation, in terms of percentage time spent in the target INR range, and rate of complications also varies between countries. In The Netherlands the percentage time in target range is highest (78.5%) and the estimated rates of bleeding and stroke are the lowest (1.4 and 0.1%, respectively). The reason for this might be that in The Netherlands coumarin therapy is managed by specialised anticoagulation clinics. However, differences in study designs and populations may have important confounding effects. The costs associated with coumarin therapy and the management of these complications also differ appreciably.

Differences in the management and quality of anticoagulant care could influence the effectiveness and cost–effectiveness of pre-treatment genotyping. The greatest health benefit (and highest probability of being cost-effective) would be expected in countries where anticoagulant care is less well organised or the quality is low; whereas the least health benefit would be achieved where anticoagulation care is already of a high standard. Nevertheless, genotyping might still be a cost-effective (or cost-saving) strategy in countries where anticoagulant care is well organised if a consequence is that less INR measurements are required when patients reach a stable dose earlier with genotyping. If possible, country-specific data on the effectiveness of genotyping should be used as well as country-specific costs in a cost–effectiveness analysis.

This article is the first to systematically describe the differences in organization and costs of anticoagulant care in different European countries. However, more information was available for some countries than for others. In The Netherlands, for example, the FNT analyses and publishes the percentage time in target range and the occurrence of complications for most anticoagulation clinics every year and thereby provides reliable and current information on routine practice. For some other countries, we had to rely on information from clinical trials, which may not be generalizable to routine practice. The data on costs were similarly derived from different sources, and will vary according to perspective, year of analysis and the items included in the calculations of overall costs.

CONCLUSION

Many differences exist between European countries in the organization of anticoagulation services, and the costs of anticoagulant therapy with coumarin derivatives. Because of these differences, it is likely that the cost–effectiveness of pharmacogenetic-guided dosing of coumarin derivatives will vary considerably among countries. Consequently, appropriate methods are necessary to deal with these differences. These methods should include appropriate use of country-

specific information about current care and its costs. In addition, a good understanding of how pharmacogenetic-guided dosing would be integrated into care is essential in estimating its cost–effectiveness in a particular country.

FUTURE PERSPECTIVE

Currently, several large trials are ongoing to investigate the effectiveness of pharmacogenetic-guided coumarin dosing [6,7]. The COAG trial investigates genotyping in different centres in the USA (NCT00839657 [116]) and the EU-PACT trial in different European countries (NCT01119261, NCT01119274, NCT01119300 [117–119]). The results of the EU-PACT trial could be used together with the country-specific information in the present study to analyse the cost–effectiveness of this treatment strategy in different countries. This could help decision makers to decide whether to implement pharmacogenetics in coumarin therapy or not.

Pharmacogenetics is not the only development in the area of anticoagulant therapy. Recently, new drugs (e.g., direct thrombin inhibitors and factor Xa inhibitors) have been developed for anticoagulant treatment and these might be good alternatives for warfarin [83,84]. One of the advantages of these drugs is the fact that they do not require frequent monitoring (which is often considered burdensome for the patient), while the lack of a biomarker to monitor the extent of anticoagulation can also be seen as a disadvantage. Other disadvantages include an anticipated decrease in therapy adherence, interactions with other drugs and the fact that no antidote yet exists. Another issue is the costs of these new drugs, which are more expensive than coumarin derivatives. With the current climate of increasing healthcare expenses and the need to cut costs, the budget impact and cost–effectiveness of implementing these new drugs should be investigated. The data in this article provide information for future analyses of the cost–effectiveness of genotyping versus standard care, but can also be used to inform future analyses of the cost–effectiveness of the new oral anticoagulants. Shah *et al.* demonstrated that the cost–effectiveness of dabigatran, a direct thrombin inhibitor, versus warfarin was dependent of the time spent in target INR range with warfarin [85]. With a high percentage time in range, dabigatran appeared to be less cost effective than when this percentage was low. You *et al.* also found that dabigatran would be less cost-effective with better INR control in warfarin users, in a cost–effectiveness analysis of dabigatran versus pharmacogenetic-guided warfarin dosing [86]. Pink *et al.* also concluded that dabigatran will only be cost-effective for patients with an increased risk of stroke and for patients on coumarin anticoagulants with a low percentage time in the INR target range [67]. When genotyping improves the time spent in the target range, this could be a more cost-effective option than using the new drugs. This should be investigated in future cost–effectiveness analyses. Currently, there is not enough evidence about the effect of genotyping or the effect of the new oral anticoagulants to make any recommendations regarding this.

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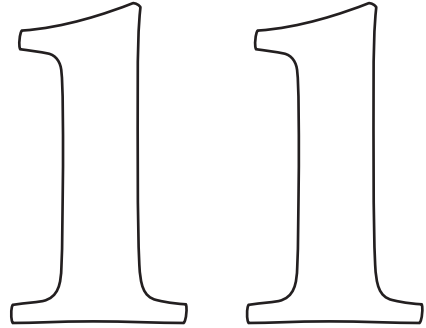
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COST-EFFECTIVENESS OF NEW ORAL ANTICOAGULANTS FOR STROKE PREVENTION IN PATIENTS WITH ATRIAL FIBRILLATION IN TWO DIFFERENT EUROPEAN HEALTHCARE SETTINGS

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ABSTRACT

Objectives: To investigate the cost-effectiveness of apixaban, rivaroxaban and dabigatran, compared to coumarin derivatives for stroke prevention in patients with atrial fibrillation in a country with specialised anticoagulation clinics (The Netherlands) and in a country without these clinics (the United Kingdom).

Methods: A decision-analytic Markov model was used to analyse the cost-effectiveness of apixaban, rivaroxaban and dabigatran compared to acenocoumarol in The Netherlands and warfarin in the United Kingdom over a lifetime horizon.

Results: In the Netherlands, the use of apixaban, rivaroxaban or dabigatran increased health by 0.36, 0.17 and 0.37 quality-adjusted life-years (QALYs), but also increased costs by €4,762, €5,621 and €5,812, respectively. The incremental cost-effectiveness ratios (ICERs) were €13,170, €32,845 and €15,816 per QALY gained. In the United Kingdom, health was increased by 0.45, 0.30 and 0.46 QALYs and the incremental costs were similar for all three new oral anticoagulants (€5,189 to €5,274). The ICERs varied from €11,400 to €16,970 per QALY gained. In The Netherlands, apixaban had the highest chance (61%) to be cost-effective at a threshold of €20,000 and in the United Kingdom this chance was 72% for both dabigatran and apixaban. The quality of care reflected in time in therapeutic range had an important influence on the ICER.

Conclusions: Apixaban, rivaroxaban and dabigatran are cost-effective alternatives to warfarin in the United Kingdom, while in The Netherlands, only apixaban and dabigatran could be considered cost-effective. The cost-effectiveness of the new oral anticoagulants is largely dependent on the setting and quality of local anticoagulant care facilities.

INTRODUCTION

Patients with atrial fibrillation (AF) are at increased risk of stroke and other thromboembolic events. Therefore an anticoagulant is often indicated to decrease this risk [1]. Vitamin K antagonists (or coumarin derivatives) have been used for many years as oral anticoagulants for stroke and systemic embolism (SE) prevention in patients with AF. These drugs have a small therapeutic window and a large inter-individual and intra-individual variability in dose response. Frequent monitoring of the anticoagulant effect (expressed as International normalised ratio, INR) is therefore required [2]. Recently, new oral anticoagulants have become available for the prevention of stroke and SE in patients with AF. These drugs do not require such monitoring and have been shown in randomised controlled trials to be non-inferior or even superior to warfarin in the prevention of stroke and SE [3-6].

Dabigatran is a direct thrombin inhibitor and at a dose of 150 mg this anticoagulant is associated with a lower rate of stroke and SE and a similar bleeding rate if compared to warfarin [3,4]. Apixaban is a factor Xa inhibitor and was shown to be superior to warfarin in the prevention of stroke and SE as well as

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bleeding [5]. Another factor Xa inhibitor, rivaroxaban, was non-inferior to warfarin for the prevention of stroke and SE and fewer intracranial or fatal bleeding events occurred in patients using this drug [6]. All three new oral anticoagulant drugs are considered useful alternatives to coumarin derivatives [3-6]. However, since the costs of these new drugs are considerably higher than the costs of coumarin anticoagulants, it is important to investigate their cost-effectiveness carefully.

The cost-effectiveness of dabigatran has been investigated in several studies and it was shown to be cost-effective [7-9]. When the quality of the warfarin treatment is higher (a higher percentage of time is spent in the therapeutic INR range), the chance that dabigatran is cost-effective is lower. Because the quality of the treatment with coumarin derivatives varies across different countries and different healthcare settings, the cost-effectiveness of the new oral anticoagulants needs to be investigated in different settings [10]. In the Netherlands, treatment with coumarin derivatives is monitored and guided by specialised anticoagulation clinics. The percentage time patients spent in the therapeutic INR range in this country is 76-79% for patients using short or long-term (2 months to lifetime) acenocoumarol, which is the most frequently used coumarin anticoagulant in The Netherlands [11]. In the United Kingdom, warfarin is most frequently used and many warfarin users are treated by general practitioners [12]. The percentage time spent in the therapeutic INR range is lower than in the Netherlands; one estimate was approximately 63% [13]. The aim of this study is therefore to investigate the cost-effectiveness of apixaban, rivaroxaban and dabigatran, compared to coumarin derivatives in a country with specialised anticoagulation clinics (The Netherlands) and in a country where the treatment of many patients with coumarin anticoagulants occurs in a primary care setting rather than a specialised anticoagulation clinic (the United Kingdom).

METHODS

Model structure

A decision-analytic Markov model was used to analyse the cost-effectiveness of the three new oral anticoagulants (apixaban, rivaroxaban and dabigatran) compared to coumarin derivatives (acenocoumarol in The Netherlands and warfarin in the United Kingdom). The model was developed using TreeAge software (TreeAge Pro 2012). The base-case analysis consisted of a hypothetical cohort of patients with AF, aged 70 years, initiating oral anticoagulant therapy.

Figure 1 shows the decision tree with the four treatment options. The decision-analytic Markov model consisted of nine health states: Healthy with AF, ischaemic stroke (IS), transient ischaemic attack (TIA), myocardial infarction (MI), systemic embolism (SE), intracranial haemorrhage (ICH), extra cranial haemorrhage (ECH), disability and death. All patients entered the model in the 'healthy with AF' state and could move to one of the other states at monthly intervals. Patients with an IS had a 37% chance of dying and 32% chance of
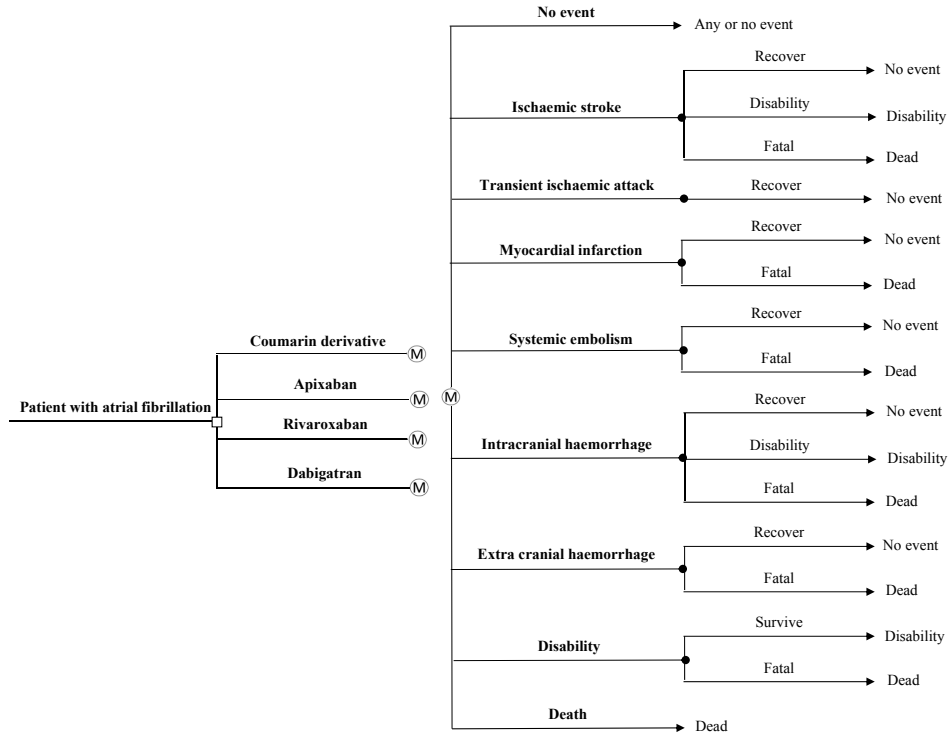
Figure 1. Schematic representation of the decision tree and Markov model. Patients initiating oral anticoagulant therapy can be treated by one of the four drugs with different chances of developing adverse events.

disability [5,6]. The chance that an ICH would be disabling was 50% and that it would be fatal was 44% [11,14]. MI and ECH were fatal in 16% and 7% of the cases, respectively [11,15,16]. We assumed a similar percentage of fatal cases (7%) in SE as in ECH and a mortality rate of 5.6% in patients in the disability state [17]. Age-specific mortality rates were taken into account for all patients. Input parameters of the model for both The Netherlands and the United Kingdom are shown in Table 1.

Clinical event rates

Annual rates of clinical events of the new oral anticoagulants were derived from three large randomised controlled trials. Data from the ARISTOTLE trial were used for event rates of a apixaban at a dose of 5 mg twice daily [5], data from the ROCKET-AF trial for rivaroxaban 20 mg once daily [6] and from the RE-LY trial for dabigatran 150 mg twice daily [3,4]. To adjust for differences in baseline risks between the three trials the indirect comparison method by Bucher *et al.* was used [18]. Event rates for rivaroxaban and dabigatran were calculated by multiplying the relative treatment effects by the event rates of the warfarin arm in the apixaban trial.

To correct for differences in quality of coumarin anticoagulant care, the rates of

Table 1. Model input parameters for both the Netherlands and the United Kingdom

Parameter	Base case	Range	Source
Age at start of treatment	70	60 to 80	Assumption
Outcome of events (if occurring) %			
Fatal stroke	37	0.30 to 0.44	[5,6]
Disabling stroke	32	0.26 to 0.38	[5,6]
Fatal transient ischaemic attack	0	-	Assumption
Fatal systemic embolism	7	0.056 to 0.084	Assumption
Fatal myocardial infarction	16	0.13 to 0.19	[15,16]
Fatal intracranial haemorrhage	44	0.35 to 0.53	[11]
Disabling intracranial haemorrhage	50	0.40 to 0.60	[14]
Fatal extracranial haemorrhage	7	0.056 to 0.084	[11]
Monthly mortality rate disability state	5.6	0.04 to 0.07	[17]
QALYs and decrements			
Atrial fibrillation	0.81	0.67819 to 0.91373	[22]
Use of vitamin K antagonist	-0.013	-0.002 to -0.033	[22]
Use of new oral anticoagulant	-0.006	-0.004 to -0.007	[20]
Use of aspirin	-0.002	-0.000 to 0.006	[20]
Stroke	-0.1385	-0.11843 to -0.15998	[22]
Transient ischaemic attack	-0.10322	-0.09912 to -0.11894	[22]
Systemic embolism	-0.1199	-0.10224 to -0.13880	[22]
Myocardial infarction	-0.1247	-0.10645 to -0.14356	[22]
Intracranial haemorrhage	-0.1814	-0.15500 to -0.20885	[22]
Extracranial haemorrhage	-0.06	-0.02 to -0.10	[17]
Disability	-0.374	-0.160 to -0.588	[17]

clinical events were based on the time spent in the therapeutic INR range. The risks of thromboembolic and haemorrhagic events associated with different INR ranges were derived from a meta-analysis by Oake *et al.* [19]. The proportion of thromboembolic events that were stroke, MI or SE and the proportion of haemorrhagic events that were intracranial or extracranial were derived from the warfarin arms of the three trials of the new oral anticoagulants (weighted average) [3-6]. As in previous cost-effectiveness studies, we assumed that 28% of ischaemic strokes were TIA [8,20]. In our model we used a percentage time spent in the target range of 76% for the Netherlands and 63% for the United Kingdom after the initiation period (2 months) [11,13]. In the first month of treatment this percentage was 50% (own data, not published [21]). During the first 2 months 75% of the out-of-range INRs were subtherapeutic (INR<2) and after the initiation period out-of-range INRs were more often

supratherapeutic (70% INR>3) (own data, not published [21]). Patients on either one of the new oral anticoagulants or on coumarin therapy were assumed to switch to aspirin after an ICH [1]. The annual rates of clinical events of the different treatment options are shown in Table S1 (Supplement).

Quality of life and costs

The baseline quality of life in our model was 0.81 for patients with AF [22]. A decrement of 0.013 was applied for acenocoumarol or warfarin use and a decrement of 0.006 for apixaban, rivaroxaban or dabigatran use. Decrements were also ascribed when patients experienced an adverse event. Table 1 shows QALY values and decrements for the different health states.

The frequency of INR measurements has been estimated at 20.4 per year in the Netherlands and 10 per year in the United Kingdom [11,23]. We assumed 4 extra measurements in the first month and 1 extra measurement after an adverse event. Costs of an INR measurement were derived from the Dutch healthcare authority tariff and from a report of the National Institute for Health and Care Excellence (NICE) [24,25]. Monthly drug costs were estimated using data from the Dutch healthcare insurance board and the NICE report [25,26]. Costs of the drugs and adverse events are shown in Table 2. 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 since most of the cost differences were expected to be found in this sector. Effects were discounted at an annual rate of 1.5% for The Netherlands and 3.5% for the United

Kingdom and costs at an annual rate of 4% and 3.5% respectively, according to the national guidelines [27,28]. Because of the different guidelines regarding discount rates in the two countries, we also performed the analysis without discounting.

Base case and sensitivity analyses

Base-case estimates of the costs and QALYs of apixaban, rivaroxaban, dabigatran and the coumarin derivative were determined. Also several sensitivity analysis were 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 or decreased and increased by 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 the new oral anticoagulants. Dirichlet distributions were used to vary the probabilities of 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 uniform distribution was used to vary the frequency of INR measurements and a normal distribution for the percentage time spent in the therapeutic INR range.

In the United Kingdom, NICE expressed a willingness to pay threshold of £20,000-30,000 per QALY gained [29]. The Dutch guidelines do not express such a threshold because it depends on different factors, but €20,000 was often used in

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Table 2. Country specific model input parameters

Parameter	The Netherlands		United Kingdom	
	Base case (range)	Source	Base case (range)	Source
Time in therapeutic range (%)				
Month 1 and 2	50 (40-60)	Own data & [11]	50 (40-60)	Own data & [11]
Month 3 and later	76 (66-86)	Own data & [11]	63 (53-73)	[13]
Number of INR measurements (monthly)				
Maintenance phase	1.7 (0.7-1.7)	[11]	0.83 (0.67-1)	[23]
Extra during first month	4 (2-6)	Assumption	4 (2-6)	Assumption
Costs, euro				
Coumarin (monthly)	1.50 (1.20-1.80)	[26]	4.47 (3.58-5.37)	[25]
Apixaban (monthly)	68 (55-82)	[26]	82 (65-98)	[25]
Rivaroxaban (monthly)	64 (52-77)	[26]	78 (63-94)	[25]
Dabigatran (monthly)	68 (55-82)	[26]	82 (65-98)	[25]
Aspirin (monthly)	2.83 (2.26-3.40)	[26]	3.36 (2.68-4.03)	[33]
INR measurements (per visit)	10.38 (8.30-12.46)	[24]	30.40 (24-36)	[25]
Stroke	19,652 (15,722-23,583)	[34]	14,750 (11,800-17,700)	[35]
Transient ischaemic attack	949 (759-1,139)	Buisman*	1,115 (892-1,338)	[36]
Systemic embolism	990 (792-1188)	[37]	2,182 (1,746-2,618)	[36]
Myocardial infarction	18,624 (14,899-22,349)	[38]	1,852 (1,481-2,222)	[36]
Intracranial haemorrhage	25,047 (20,038-30,057)	[39]	14,531 (11,625-17,437)	[35]
Extracranial haemorrhage	13,690 (10,952-16,428)	[40]	2,256 (1,805-2,708)	[36]
Disability** (monthly)	480 (384-576)	[34]	780 (624-936)	[35]
Discount rate (yearly, %)				
Costs	4 (0-8)	[27]	3.5 (0-6)	[28]
Effects	1.5 (0-3)	[27]	3.5 (0-6)	[28]

* forthcoming, ** after stroke or intracranial haemorrhage

previous reimbursement decisions [30]. We therefore studied the chance that the new oral anticoagulants would be cost-effective at thresholds of €20,000 and €36,000 (approximately £30,000), but also varied this threshold over a wider range in a cost-effectiveness acceptability curve.

RESULTS

Base case

Figure 2 shows the first-year incidence of the clinical events per 100 patient-years for acenocoumarol in The Netherlands, warfarin in the United Kingdom and apixaban, rivaroxaban or dabigatran in both countries. All three new oral anticoagulants had a lower stroke rate than acenocoumarol and warfarin. ECHs were more frequent in rivaroxaban and dabigatran, but less frequent in apixaban than in either of the coumarin anticoagulants.

Table 3 shows the results of the cost-effectiveness analyses of the new oral anticoagulants compared to a coumarin derivative in The Netherlands and the United Kingdom. In the Netherlands, the use of apixaban increased costs by €4,762, the use of rivaroxaban by €5,621 and dabigatran by €5,812. QALYs were increased by 0.36, 0.17 and 0.37, respectively. The incremental cost-effectiveness ratio (ICER) was €13,170 per QALY gained for apixaban, €32,845 per QALY gained for rivaroxaban and €15,816 per QALY gained for dabigatran. In the United Kingdom the incremental costs were similar for all three new oral anticoagulants (€5,189 to €5,274). Apixaban use increased QALYs by 0.45, rivaroxaban by 0.31 and dabigatran by 0.46. The ICER of apixaban (€11,655 per QALY gained) and dabigatran (€11,400 per QALY gained) were somewhat lower than that of rivaroxaban (€16,970 per QALY gained). The costs per life year gained of apixaban, rivaroxaban and
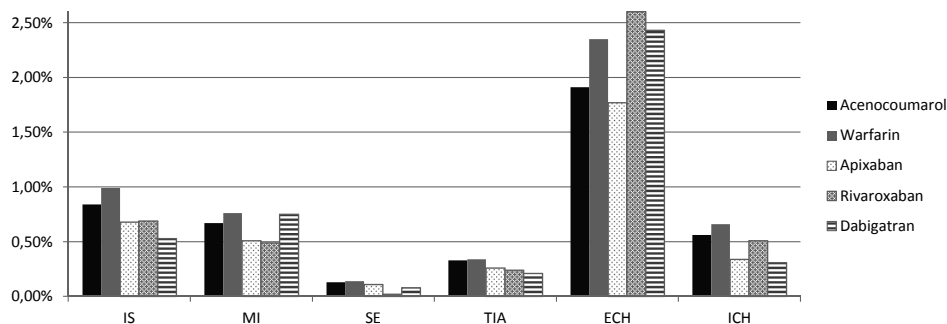
Figure 2. First year incidence of clinical events per 100 patient-years. IS=ischaemic stroke, TIA=transient ischaemic attack, SE=systemic embolism, MI=myocardial infarction, ICH=intracranial haemorrhage, ECH=extra cranial haemorrhage. Acenocoumarol as used in the Netherlands and warfarin as used in the United Kingdom.

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

Treatment	Total costs (€)	Total QALYs	Δ costs (€)	Δ QALYs	ICER (€/QALY gained)
			Compared to coumarin anticoagulant		
The Netherlands					
Acenocoumarol	9,676 (13,428)	9.629 (10.968)		Reference therapy	
Apixaban	14,438 (20,160)	9.991 (11.403)	4,762 (6,732)	0.362 (0.435)	13,170 (15,474)
Rivaroxaban	15,328 (21,332)	9.802 (11.171)	5,652 (7,904)	0.172 (0.203)	32,845 (38,939)
Dabigatran	15,488 (21,628)	9.997 (11.410)	5,812 (8,200)	0.367 (0.443)	15,816 (18,531)
The United Kingdom					
Warfarin	7,845 (10,436)	8.042 (10.706)		Reference therapy	
Apixaban	13,119 (17,638)	8.494 (11.403)	5,274 (7,201)	0.453 (0.696)	11,655 (10,341)
Rivaroxaban	13,035 (17,475)	8.347 (11.171)	5,190 (7,039)	0.306 (0.464)	16,970 (15,162)
Dabigatran	13,054 (17,549)	8.498 (11.410)	5,208 (7,113)	0.457 (0.704)	11,400 (10,106)

Results using the country specific discount rates are shown. In grey, also the non-discounted results are shown.

dabigatran were €14,353, €54,420 and €17,284, respectively in The Netherlands and €11,544, €18,471 and €11,324 in the United Kingdom.

Sensitivity analyses

Figures S1 to S6 (Supplement) show the tornado diagrams summarizing the results of the one way sensitivity analysis. These diagrams depict the 10 parameters with the largest influence on the ICER. In the Netherlands, the percentage time in range (varied from 66-86%) had the largest impact on the cost-effectiveness results for all three new oral anticoagulants. This parameter had a smaller impact in the United Kingdom (varied from 53-73%), where the risk of ICH at an INR of 3-5 (varied from 0.39-5.18) had the largest impact for apixaban and dabigatran and the second largest impact for rivaroxaban. The probability of ICH (varied from 0.33-0.85) had the largest impact on the cost-effectiveness results of rivaroxaban.

In the probabilistic sensitivity analysis, the new oral anticoagulants were more costly and more effective than coumarin anticoagulants in the majority of the simulations (figure 3). In The Netherlands, apixaban had the highest chance to be cost-effective at a willingness to pay threshold of €20,000 or €36,000 per QALY gained (61% and 76%, respectively). The ICER was below these thresholds in 55% and 74% of the simulations for dabigatran and in 34% and 48% of the simulations for rivaroxaban, respectively. In the United Kingdom, apixaban and dabigatran had similar chances to be cost-effective at a willingness to pay threshold of €20,000 or €36,000 per QALY gained (for both drugs 72% and 88%, respectively). These chances were lower for rivaroxaban (52% and 70%, respectively). Figure 4 shows
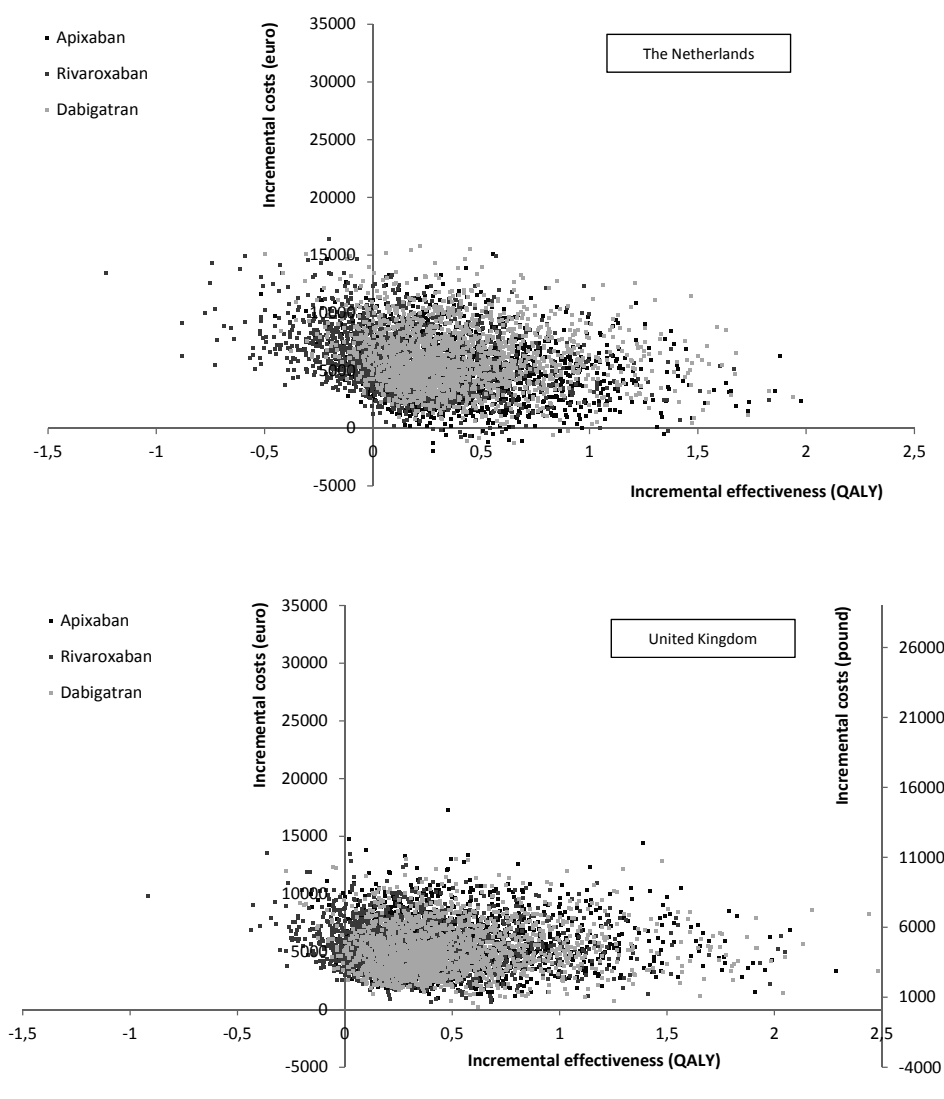
Figure 3. Scatter plots reflecting the uncertainty in the differences in costs and effectiveness between the new oral anticoagulants and coumarin anticoagulants (based on probabilistic sensitivity analysis)

the probability that any of the different oral anticoagulants would be the most cost-effective option in The Netherlands or in the United Kingdom over a range of likely thresholds. In The Netherlands, apixaban is the most cost-effective option when the willingness to pay is €20,000 per

QALY gained or higher. Dabigatran has a lower chance to be the most cost-effective at this threshold, but is close to apixaban at higher thresholds. Rivaroxaban does not have a high chance of being the most cost-effective option. The results for the United Kingdom show that dabigatran
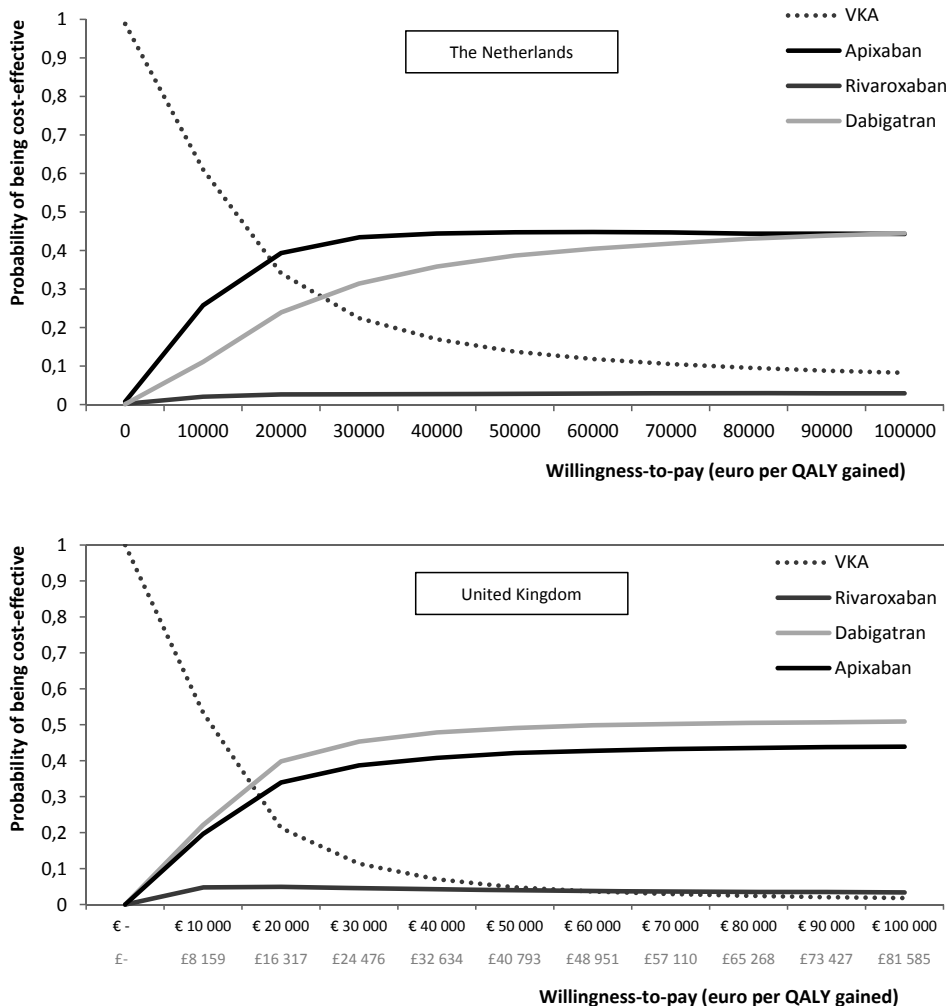
Figure 4. Cost-effectiveness acceptability curve for The Netherlands and the United Kingdom.

has a relatively high chance of being the most cost-effective when the willingness to pay exceeds €20,000 (or 16,317 pounds), closely followed by apixaban.

DISCUSSION

Our results confirm that apixaban, rivaroxaban and dabigatran are all cost-effective alternatives to warfarin in the United Kingdom. In The Netherlands, however, the incremental costs per QALY gained for these new oral anticoagulants are higher and rivaroxaban could not be considered cost-effective at a willingness

to pay of €20,000 per QALY gained. The percentage time spent in the therapeutic INR range had an important effect on the cost-effectiveness ratio. These results indicate that the cost-effectiveness of the new oral anticoagulants is largely dependent on the setting and quality of local anticoagulant care facilities.

To our knowledge this is the first study comparing the cost-effectiveness of the new oral anticoagulants in two different countries with different healthcare settings. Moreover, the cost-effectiveness of these new drugs in the Dutch setting has not been published before. For the United Kingdom, Pink *et al.* showed a base case ICER for dabigatran of £23,082 (approximately €28,000) and a 60% chance that this drug would be cost-effective at a threshold of £30,000 [9]. Alternatively, the base case ICER in a study by Kansal *et al.* was £4,831 (approximately €5,900) [31]. This difference is probably caused by differences in cost and quality of life estimates. For example, higher long-term costs of stroke and higher warfarin monitoring costs were used in the study by Kansal *et al.*. In our study, the ICER of dabigatran in the United Kingdom was somewhere in between at €11,400 per QALY gained. Also, this is one of the first studies investigating the cost-effectiveness of the three new oral anticoagulants together. Harrington *et al.*, studied their cost-effectiveness in the setting of the United States and found that the ICER of all three new oral anticoagulants was below their willingness to pay threshold [32].

One thing that Harrington *et al.* did not do is adjust the clinical event rates for differences in baseline risks between the three trials. Although we adjusted the clinical event rates from the three trials for differences in baseline risks, uncertainty remains about the comparison between the three different new oral anticoagulants. Because the three drugs have not been studied in a head-to-head trial, it was not possible to investigate the cost-effectiveness of these drugs using information from a direct comparison. Another limitation is that the follow-up in the three trials was approximately 2 years. We extrapolated this data to a lifetime horizon, assuming the event rates would remain stable after 2 years. Lastly, because no official cost-effectiveness threshold exists in The Netherlands, it is difficult to state whether or not a new therapy will be considered as cost-effective. This threshold is influenced by several factors, for example life expectancy [30].

Our results indicate that country or healthcare setting specific analyses are important to study the cost-effectiveness of new oral anticoagulant compared to coumarin derivatives. Because of differences in costs of the drugs or differences in the treatment costs of clinical events, the cost-effectiveness of drugs can differ between countries. But more important in this case is the difference in healthcare setting and quality of the treatment with coumarin derivatives. In the Dutch setting of anticoagulant clinics, with a high percentage time spent in the therapeutic INR range, the new drugs are less cost-effective than in the English setting where patients are treated by the general practitioner and spend less time in the therapeutic INR range. A strength of this study is that we compared the

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new oral anticoagulants with coumarin derivatives in two different countries using the same model. Because the analyses are performed in the same way, the results are easier to compare than in two different studies. Although different coumarin anticoagulants were used in the two countries, we believe this would not cause differences in our results because of the similarity between different coumarin anticoagulants.

In the United Kingdom apixaban, rivaroxaban and dabigatran all appear to be cost-effective alternatives to warfarin, increasing health at acceptable costs.

Although all three new oral anticoagulants also lead to improved health in The Netherlands, the incremental costs of rivaroxaban are higher than what may be regarded as acceptable. Dabigatran and apixaban do seem to be the cost-effective options in The Netherlands. In both countries the use of new oral anticoagulants will impact the healthcare budget. Whether it is better to spend the budget on new oral anticoagulants or on improving the quality of current care with coumarin derivatives (by for example personalised dosing) is an interesting question for debate.

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Table S1. Yearly incidence of events per 100 patient years

Base case (range)	IS	TIA	SE	MI	ICH	ECH	Source
New oral anticoagulant							
Apixaban	0.70 (0.56-0.85)	0.27 (0.22-0.33)	0.09 (0.04-0.18)	0.53 (0.40-0.71)	0.33 (0.24-0.46)	1.79 (1.54-2.11)	1
Rivaroxaban	0.71 (0.52-0.96)	0.27 (0.20-0.37)	0.03 (0.01-0.09)	0.49 (0.33-0.72)	0.53 (0..-0.85)	2.60 (2.12-3.19)	1,2
Dabigatran	0.57 (0.41-0.79)	0.22 (0.16-0.31)	0.08 (0.03-0.22)	0.76 (0.51-1.16)	0.32 (0.19-0.53)	2.42 (1.95-3.01)	1,3,4
Vitamin K antagonist							
INR below range	2.68 (1.36-5.28)	1.04 (0.53-2.04)	0.37 (0.19-0.72)	2.01 (1.02-3.96)	0.09 (0.07-0.12)	0.31 (0.23-0.39)	1-5
INR within range	0.57 (0.26-1.19)	0.22 (0.10-0.46)	0.08 (0.04-0.16)	0.43 (0.20-0.89)	0.30 (0.12-0.78)	1.00 (0.39-2.62)	1-5
INR above range (<5)	0.88 (0.26-2.77)	0.34 (0.10-1.07)	0.12 (0.04-0.38)	0.66 (0.20-2.08)	1.40 (0.39-5.18)	4.70 (1.31-17.3)	1-5
INR above range (>5)	1.98 (1.14-3.48)	0.77 (0.44-1.34)	0.27 (0.16-0.47)	1.49 (0.86-2.61)	5.91 (2.23-15.6)	19.79 (7.5-52.3)	1-5
Alternative treatment							
Aspirin	2.16 (1.44-3.17)	0.84 (0.56-1.23)	0.40 (0.15-3.33)	0.90 (0.54-1.60)	0.40 (0.21-1.05)	0.90 (0.54-1.49)	6

IS=ischaemic stroke, TIA=transient ischaemic attack, SE=systemic embolism, MI=myocardial infarction, ICH=intracranial haemorrhage, ECH=extra cranial haemorrhage

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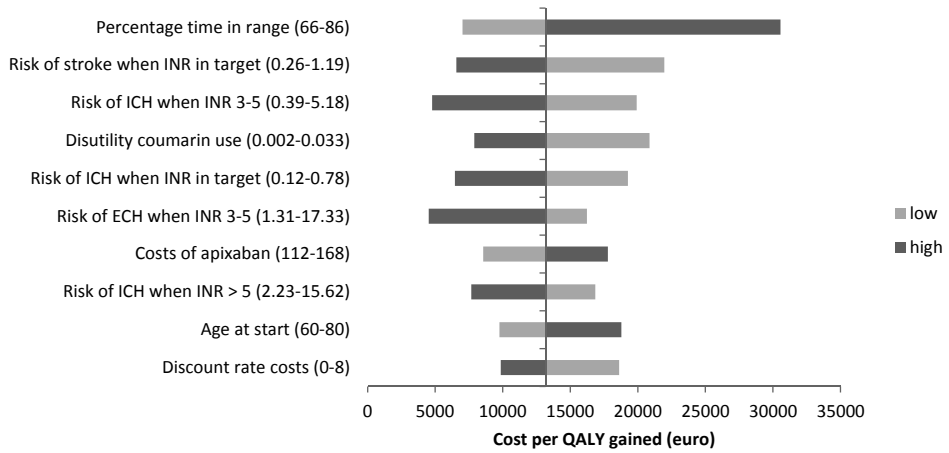
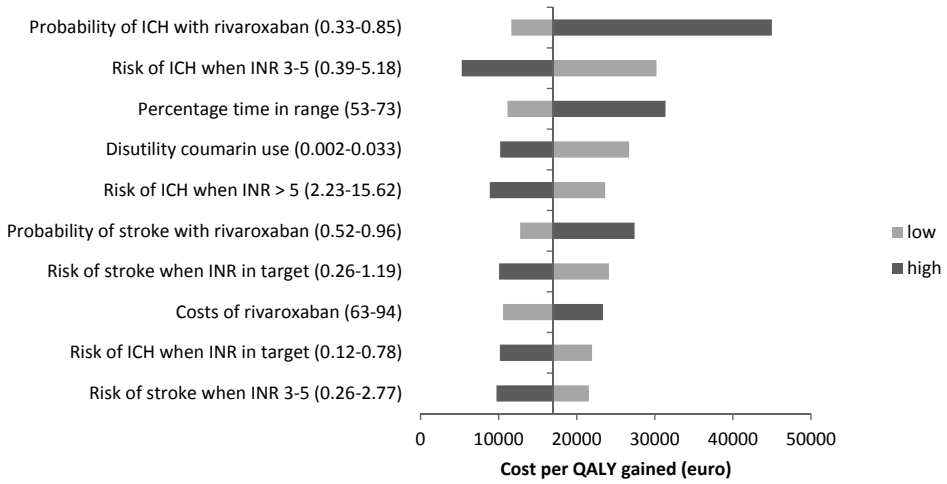**Figure S1.** Tornado diagram of apixaban vs. acenocoumarol in The Netherlands.
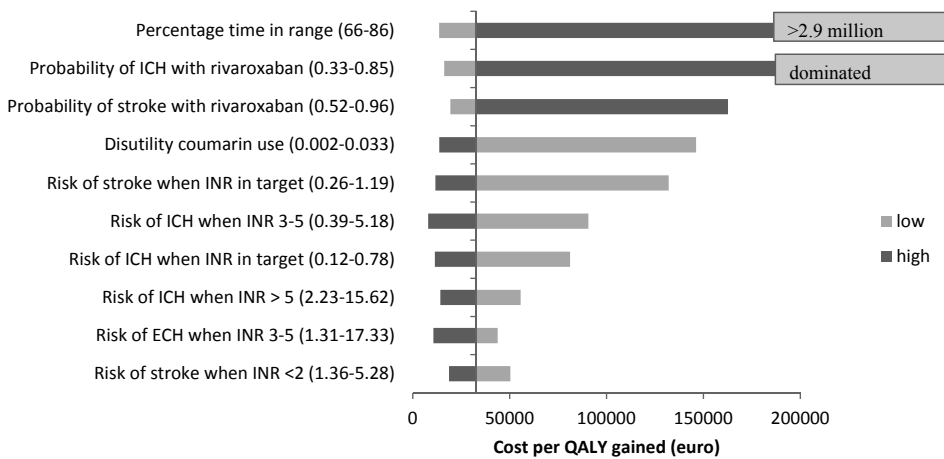
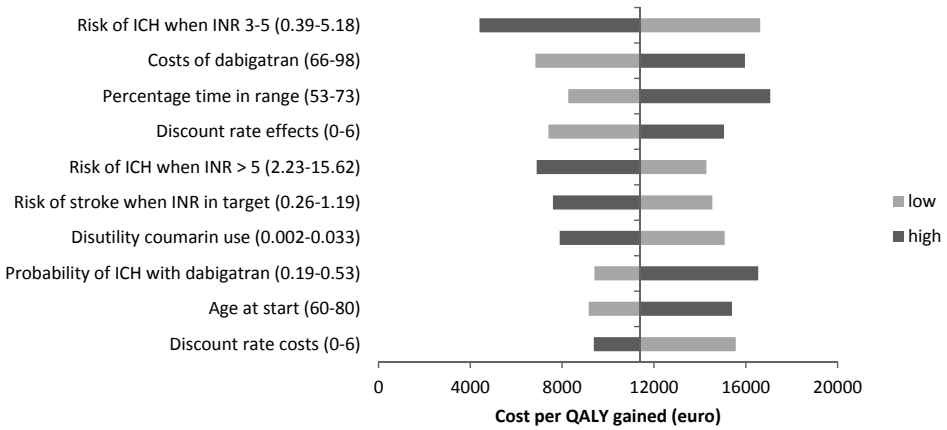**Figure S2.** Tornado diagram of rivaroxaban vs. acenocoumarol in The Netherlands.
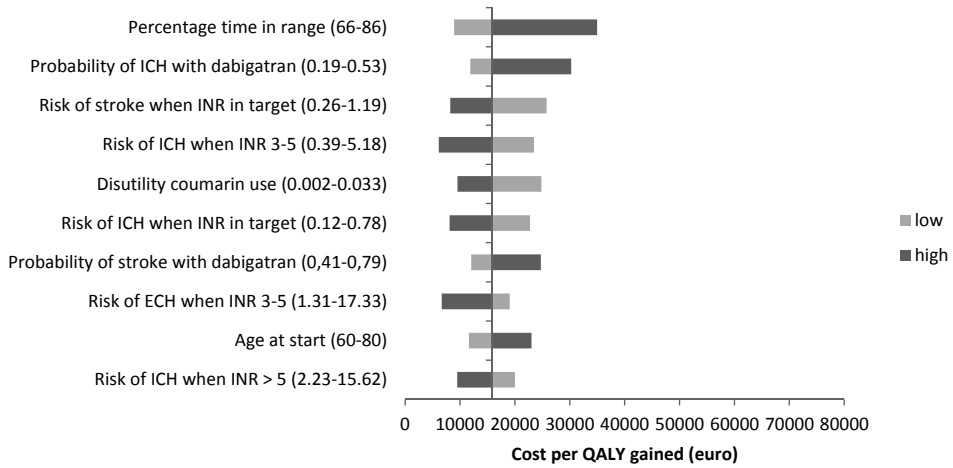
Figure S3. Tornado diagram of dabigatran vs. acenocoumarol in The Netherlands.
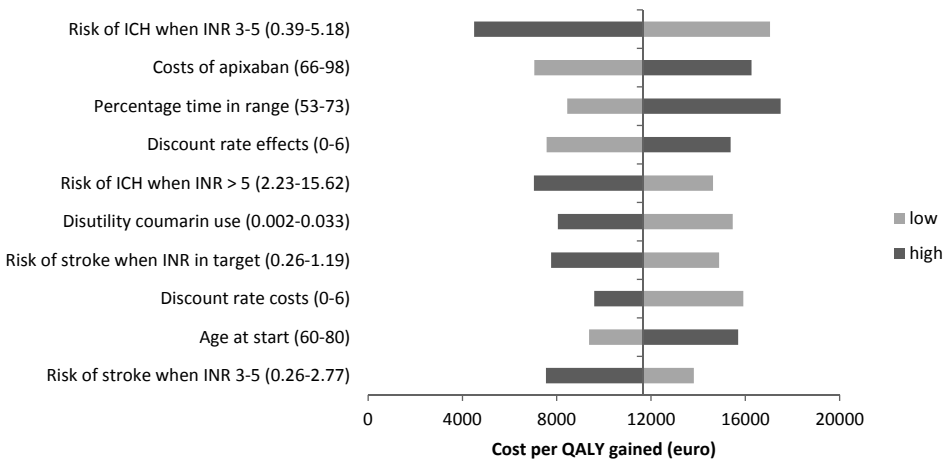
Figure S4. Tornado diagram of apixaban vs. warfarin in the United Kingdom.

Figure S5. Tornado diagram of rivaroxaban vs. warfarin in the United Kingdom.

Figure S6. Tornado diagram of dabigatran vs. warfarin in the United Kingdom.

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GENERAL DISCUSSION

INTRODUCTION

Coumarin derivatives are widely used oral anticoagulants. In Europe, warfarin, phenprocoumon and acenocoumarol are frequently used. In 2009, approximately 385.000 patients were treated with acenocoumarol or phenprocoumon in The Netherlands and this number increased to approximately 430.000 in 2011 [1]. The most common indication for coumarin anticoagulant therapy is atrial fibrillation, followed by venous thromboembolism. Due to the ageing of the population, the number of patients with atrial fibrillation is expected to increase further in the coming years [2]. Patients with atrial fibrillation have an increased risk of stroke and systemic embolism. Coumarin anticoagulant treatment can reduce this risk by 60% [3]. However, while reducing the risk of stroke and other thromboembolic events, treatment with coumarin derivatives increases the risk of bleeding. To balance the risk of thromboembolic events and the risk of bleeding, frequent monitoring of the anticoagulant effect is required, which is done by measuring the International Normalised Ratio (INR). The optimal balance between effectiveness and safety is seen when the INR is between 2 and 3 [4]. Because of the large variability in dose requirement among patients and interactions with, for example, food and other drugs, keeping the INR within this therapeutic range is difficult [5]. This causes a risk of thromboembolic and bleeding events and coumarin derivatives are therefore often associated with drug-related hospitalisation or visits to the emergency department [6,7].

One of the factors explaining the variation in dose requirement among patients is genetic variation. Single nucleotide polymorphisms (SNPs) in two genes (*CYP2C9* and *VKORC1*) can explain approximately one-third of the dose variation [8-11]. The *CYP2C9* gene codes for the main metabolizing enzyme of coumarin derivatives, CYP2C9, and the *VKORC1* gene codes for the target enzyme of coumarin derivatives, VKORC1. Information on these two genes, together with other patient characteristics such as age, height, weight, race, and use of concomitant medication can be used to predict the coumarin dose and with this information approximately 50% of dose variation can be explained [12,13]. It is expected that using a genotype-guided dosing algorithm using information on *CYP2C9* and *VKORC1* genotype can improve anticoagulation control and thereby decrease the risk of thromboembolic or bleeding events. Whether this really improves the efficacy and safety of coumarin therapy is currently being investigated in clinical trials in the United States and Europe [14,15].

Another development in anticoagulation is the use of new oral anticoagulants (direct thrombin inhibitors and factor Xa inhibitors). In a meta-analysis of three large randomised trials, the efficacy and safety of dabigatran, apixaban and rivaroxaban was investigated compared to warfarin in patients with atrial fibrillation [16]. Compared to warfarin the new oral anticoagulants reduced the risk of ischaemic stroke, haemorrhagic stroke and intracranial bleeding. The results were inconclusive for gastrointestinal bleeding and major bleeding. For the treatment of acute venous thromboembolism, the new oral anticoagulants had a similar risk of

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recurrence compared to coumarin derivatives in a different meta-analysis [17]. An advantage of these new oral anticoagulants is that the effect does not need to be monitored, which is the case with coumarin derivatives. For the treatment of acute venous thromboembolism, no initial treatment with a low molecular weight heparin is required. Patients can find it burdensome to visit the clinic often for monitoring of the coumarin treatment. For these patients, using a new oral anticoagulant might be an attractive option. The new oral anticoagulants are therefore an interesting alternative to coumarin derivatives.

As is the case for many new developments in health, improving anticoagulant therapy by genotype-guided dosing or new oral anticoagulants is likely to increase costs. Implementation of genotype-guided coumarin dosing or the use of new oral anticoagulants does not only depend on the benefit-risk ratio, but also on the support of other stakeholders, such as health insurance companies. Health care expenditures are increasing and budget allocation decisions should be made. Informing the decision makers about the additional costs that need to be incurred to gain health (preferably expressed in Quality Adjusted Life Years, QALYs) will help to select the best options for reimbursement. It is therefore important to analyse the cost per QALY gained (cost-effectiveness or cost-utility) of these new treatment options.

In this chapter we will discuss the results of this thesis in which the subjects described above are addressed. We will first describe the main findings and their relevance. Secondly, we will discuss strengths and limitations of this thesis and lastly we will consider the implications of the results.

MAIN FINDINGS AND RELEVANCE

Improving coumarin anticoagulant therapy

In the first part of this thesis different ways to improve coumarin anticoagulation control are addressed. A genotype-guided algorithm might help to predict the required coumarin dose and prescribe a personalised dose to a patient commencing coumarin therapy (chapter 2). However, after a few days of treatment, the anticoagulant effect will be checked by measuring the INR and the dose will be amended accordingly. After reaching a stable dose, the algorithm used to predict the dose will not be used anymore. We hypothesised that knowledge of the patient's genotype would still be useful after reaching a stable dose when this information can be used to determine how much the dose should be decreased or increased when the INR is above or below the target range respectively. Whether there are differences in over or underanticoagulation between the different genotypes after the initiation phase was still unknown. We found that during the first 3 months of therapy, acenocoumarol users carrying a *VKORC1* variant allele (T-allele) had a higher risk of overdosing, while carriers of the common allele (C-allele) had a higher risk of underdosing (chapter 3). Patients with a *VKORC1* TT genotype had a higher chance of a supratherapeutic INR up to the sixth month of therapy. For *CYP2C9*

there were no differences in occurrence of out-of-range INRs between the different genotypes after the first month. This suggests that after a stable dose is found and a stable INR is reached, genotype information does not predict over or underanticoagulation. These results were also seen in phenprocoumon users, where INR control was not significantly different between the *VKORC1* and *CYP2C9* genotypes after the first month (chapter 4). The value of genotype information after the first month of coumarin treatment therefore seems very limited.

One possible way to improve the prediction of the required coumarin dose would be to add more parameters to the dosing algorithm. The algorithm developed by van Schie *et al.* [18], and used in the European Pharmacogenetics of Anticoagulant Therapy (EU-PACT) study, included information on *VKORC1* and *CYP2C9* genotype, age, gender, height, weight and amiodarone use. Omeprazole and esomeprazole use also affect the phenprocoumon maintenance dose (chapter 5). On average, patients using omeprazole required a 0.49 mg lower dose and patients using esomeprazole a 0.39 mg lower dose per day compared to non-users. When the use of omeprazole or esomeprazole was included in the genotype-guided algorithm, 56.7% of dose variation could be explained. However, this was only 0.8% more than the original algorithm. Other additional factors also appear to have a limited value for dose prediction. Statins, for example, only affected acenocoumarol dose and not phenprocoumon dose [19]. Additional genetic factors, such as *CYP4F2, CYP3A4* and *GATA-4*, were not clinically relevant to include in a dosing algorithm [20,21].

Instead of predicting the dose more accurately, the effectiveness of coumarin anticoagulant therapy could be improved by increasing the adherence to these drugs. The attitude patients have towards their treatment is associated with the risk of non-adherence [22,23]. The beliefs about medicines questionnaire can be used to study the attitude of patients towards the anticoagulant therapy (chapter 6). On average, coumarin users had a positive attitude towards the therapy as they scored higher on the necessity scale than on the concerns scale. But patients with atrial fibrillation scored lower on the necessity scale than patients with venous thromboembolism and had a lower necessity-concerns differential, indicating a less positive attitude. Patients with atrial fibrillation therefore have a higher chance of non-adherence.

Country specific cost-effectiveness analyses

In the second part of this thesis the issues around the cost-effectiveness of options to improve anticoagulant therapy were addressed. Several studies on the cost-effectiveness of genotype-guided dosing of coumarin anticoagulants had been published by the end of 2009 (chapter 7). The results of these analyses varied considerably. Two factors causing large uncertainty were the effectiveness of genotyping and the costs of genetic testing. As the costs of genetic testing are expected to decrease if it is used on a larger scale, the genetic test for *VKORC1* and *CYP2C9* genotypes will probably not cost more than US$50 [24]. The uncertainty around the effectiveness is therefore currently the most important

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issue. No sufficiently powered clinical trials have been published yet, but the results are expected soon. As the primary outcome of these trials is the percentage time spent in the therapeutic INR range instead of the incidence of bleeding or thromboembolic events, this measure will also be used in models to study the cost-effectiveness. This measure was also used in a cost-effectiveness study on genotype-guided dosing of warfarin in the United States (chapter 8) [25]. Because almost all of the previously published cost-effectiveness studies focused on the United States and on warfarin, almost no information was available for the European situation. We therefore used and adapted the model described in chapter 8 to study the cost-effectiveness of genotyping for phenprocoumon in The Netherlands (chapter 9). Although more recent data was used to model the effectiveness, the uncertainty was still large.

Because anticoagulation services are organized differently in the United States than in Europe, it is important to study the cost-effectiveness of genotyping in Europe. But even in Europe, differences exist in the healthcare systems (chapter 10). In some countries, anticoagulant care is managed by specialized anticoagulation clinics, while in other countries this is done by the general practitioner (GP) or in the hospital. These differences can lead to differences in the quality and costs of care and therefore impact the cost-effectiveness of genotype-guided dosing. In a country where the anticoagulant care is less well organized and the quality of anticoagulant care is relatively low, more health benefit can be expected from genotyping than from a country with

better organized care. The probability that this new treatment option would be cost-effective will also be higher in this case. Next to the effectiveness of genotyping, the costs of, for example, medical events can differ between countries. The results of chapter 10 and 11 underline the importance of addressing these country specific issues when studying the cost-effectiveness of new treatment options for anticoagulant therapy.

An alternative to improving the coumarin anticoagulant therapy by genotype-guided dosing is to use new oral anticoagulants. The cost-effectiveness of dabigatran, apixaban and rivaroxaban compared with coumarin anticoagulants varies between countries (chapter 11). In the United Kingdom, all three new oral anticoagulants could be considered cost-effective. In The Netherlands the cost-effectiveness ratios of all new oral anticoagulants were higher than in the United Kingdom and the cost-effectiveness ratio of rivaroxaban was even higher than the willingness to pay threshold of €20,000. This difference seems to be mainly driven by the differences in time spent in the therapeutic INR range. These results confirm that the cost-effectiveness is largely dependent on the setting and quality of local anticoagulant care facilities and underlines the importance of country specific analyses. Because the comparison between two countries can be hampered by variability in methodology, clinical considerations and parameter estimates when the cost-effectiveness is studied with two different models, an analysis of different countries using the same model with only differences in country specific parameters is preferred.

STRENGTHS AND LIMITATIONS

Observational data and trial data

For most studies described in this thesis observational data has been used. An observational study was performed (pre-EU-PACT) mainly to collect data for the development of the dosing algorithms to be used in the EU-PACT trial. This pre-EU-PACT study provided us with a large observational dataset with more than one thousand Dutch acenocoumarol and phenprocoumon users. This data has been used to study the impact of genetic variation and concomitant medication on the anticoagulant effect. A limitation of this study was that the data were collected retrospectively. Because we included patients who attended the clinic during one week in 2009, very unstable patients might be underrepresented because they stopped treatment before the moment of data collection. Although the data could be considered a good representation of the Dutch clinical situation, it is less comparable with other European countries, because of differences in treatment setting and target INR range. In The Netherlands, the treatment of all patients is managed by specialized anticoagulation clinics and the quality of care is high [1,2]. Next to this, the target INR range is 2.0-3.5 instead of 2.0-3.0 as in most other countries. The percentage time within the therapeutic range of patients in the pre-EU-PACT dataset is therefore higher than in other European countries.

If compared to randomised trials, the risk of bias, such as selection and information bias and confounding is higher in observational studies. However, in our observational data, the population was very representative for the population of coumarin users, because of the few exclusion criteria and because the patients were treated according to every day practice. All patients requiring coumarin anticoagulant therapy in the low intensity category (INR 2.0-3.5) could be included in the study when they were not pregnant, breastfeeding or living in a nursing home. In the EU-PACT trial, more strict inclusion and exclusion criteria were applied. Patients should have either atrial fibrillation or venous thromboembolism and should never have been treated with coumarin derivatives before. The treatment should be for at least 12 weeks. If the genotype was already known, patients were excluded. Also pregnant or breastfeeding women were excluded, as well as patients with cognitive impairment. The lower risk of bias and confounding is an advantage of the trial data.

The EU-PACT trial was carried out in six European countries to investigate the effectiveness of pre-treatment genotyping for *CYP2C9* and *VKORC1* polymorphisms. The results are not available yet. In the United States, other trials have also been performed on pharmacogenetic warfarin dosing [26,27]. A strength of the EU-PACT study is that different coumarin derivatives were included in this study. The study was performed on warfarin in the United Kingdom and Sweden, on acenocoumarol in Greece and The Netherlands and on phenprocoumon in The Netherlands, Germany and Austria. The primary outcome is the percentage time spent with an INR between 2 and 3. Participants in The Netherlands were therefore also treated with this target INR range and therefore it will be possible to compare all countries.

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Patients in the intervention arm of the trial all received a loading and maintenance dose based on a genotype-guided algorithm. Patients in the control arm in the acenocoumarol and phenprocoumon trials received a loading dose based on a clinical algorithm including the same variables as the genotype-guided algorithm, except the genetic information. In the warfarin trial however, patients in the control arm received a standard loading dose instead of a dose based on a clinical algorithm. A larger difference between the genotype-guided dosing algorithm and standard care is expected than between the genotype-guided algorithm and a clinical algorithm because a clinical algorithm might already perform better than the standard dosing regimen. Therefore a greater benefit of the genotype-guided dosing algorithm might be expected in the warfarin trial.

Next to the percentage time in INR range, the EU-PACT study will investigate for example the number of INR measurements, quality of life and the utility of a point-of-care genotype test. This point-of-care test makes it possible to determine the *CYP2C9* and *VKORC1* genotype within 100 minutes and has not been used in clinical practice before. We validated this method using 156 samples from the UK, Sweden and The Netherlands and all genotypes were in concordance with results obtained by other methods. It is a simple test which can be performed by for example anticoagulation clinic staff without laboratory training [24].

Cost-effectiveness uncertainties

Many uncertainties exist in the studies on the cost-effectiveness of genotype-guided dosing of coumarin derivatives. As mentioned before, the effectiveness of this strategy is a major contributor to this uncertainty. Because we are still waiting for the results from large randomised trials, the studies in this thesis cannot provide a conclusion about whether or not genotyping should be implemented. For the cost-effectiveness analyses in this thesis, many assumptions were made. For example, because of the lack of information about the difference in effect of genotyping on anticoagulation control between different genotypes, we assumed a similar effect among all genotypes. In reality, genotyping will probably have the highest impact in patients requiring a very high or very low dose and less impact in a patient requiring an average dose. The cost-effectiveness will therefore depend on the prevalence of the sensitive or resistant genotypes, which varies between different populations [28]. We also assumed that genotyping would have a beneficial effect during the first six months of therapy, which is in reality probably not more than 3 months, when taking into account the results from chapter 3 and 4. Next to this, we assumed a similar effectiveness of genotype-guided phenprocoumon dosing as for genotype-guided warfarin dosing, because only data from trials on genotype-guided warfarin dosing were available. No clinical study on genotype-guided phenprocoumon dosing has been published yet.

In the cost-effectiveness study on the pharmacogenetics of phenprocoumon we used the percentage time spent in the therapeutic INR range as a surrogate endpoint for bleeding and thromboembolic events. We also used this surrogate endpoint

in the study on the new oral anticoagulants, but for the coumarin anticoagulant arm only. The time spent in different INR ranges can be linked to different risks of bleeding or thromboembolic events [4]. A more direct method using the incidence of adverse events instead of the surrogate INR might lead to less uncertainty, but the clinical trials published or currently underway are not powered to detect differences in these events. It is therefore necessary to use the INR as a surrogate endpoint in the model. An advantage of this endpoint is the possibility to vary the percentage time spent in the therapeutic INR range to reflect the differences in quality of care among different countries or settings. This proved especially useful in our study on the cost-effectiveness of new oral anticoagulants in The Netherlands and the United Kingdom. In these countries, anticoagulant care is managed differently and a different quality of coumarin anticoagulant treatment is seen, which could be reflected by a different percentage time in therapeutic INR range in the cost-effectiveness models. An assumption in this study was that the results from the clinical trials on new oral anticoagulants, with an average follow up time of approximately 2 years, could be extrapolated to the lifetime horizon of the model.

Due to the many assumptions in our cost-effectiveness analysis, it was necessary to perform several sensitivity analyses. All parameters were varied over a plausible range to determine their impact on the cost-effectiveness result. In this way, factors causing the largest uncertainty could be identified. Also, the chance that the new treatment option would be cost-effective given a certain threshold could be determined by varying multiple parameters simultaneously in a probabilistic sensitivity analysis. In The Netherlands, pharmacogenetic-guided dosing had a 76% chance of being cost-effectiveness at a willingness-to-pay threshold of €20.000 provided that the percentage time in INR range would increase by at least 6% if patients received a dose based on their genotype. The chance that the new oral anticoagulants would be cost-effective was higher in the UK than in The Netherlands.

IMPLICATIONS

Use of new oral anticoagulants

The results of this thesis show that there are different ways to improve anticoagulant therapy for patients with, for example, atrial fibrillation. It is plausible that the new oral anticoagulants will be used more widely, but that coumarin derivatives will also still be used, with or without pharmacogenetic-guided dosing. The choice between the different options will depend on the situation and the patient. The new oral anticoagulants are more effective in the prevention of stroke and can be administered as a fixed dose and patients do not need to be monitored. However, there are also some disadvantages to these new drugs. Dabigatran and apixaban have to be taken twice daily, instead of once daily, which is the case for coumarin derivatives or rivaroxaban. This could have a negative effect on the patient adherence, together with the fact that the treatment is not monitored. No biomarker

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is currently available for monitoring. Another disadvantage is that patients with renal insufficiency have an increased risk of bleeding when using dabigatran, because of the prolonged half-live [29]. If a bleeding occurs or when emergency surgery is performed, no specific antidote is available yet. The use of Prothrombin Complex Concentrate may be considered, but there is currently limited evidence supporting this [30]. In the RE-LY trial, an increased risk of myocardial infarction was seen in the group of patients on dabigatran [31], although this difference was not statistically significant in a re-analysis of the data after identification of additional events [32]. In a recent meta-analysis including dabigatran, apixaban, rivaroxaban, betrixaban and edoxaban for atrial fibriallation, venous thromboembolism, orthopaedic surgery or acute coronary syndrome, the new drugs were associated with an increased risk of gastrointestinal bleeds [33].

Although the new oral anticoagulants are considered to be effective and safe at a fixed dose, personalised dosing of these drugs might also be useful in the future. For example, it is recommended that patients older than 80 years receive a lower dabigatran dose than younger patients (110 mg twice daily instead of 150 mg twice daily) [34]. Although there is not much evidence on the pharmacogenetics of the new oral anticoagulants yet, this might also play a role. A first genome wide association study identified 2 loci (*CES1* and *ABCB1*) associated with the pharmacokinetics of dabigatran [35]. The authors stated that the possibility exists that genotyping could be used to tailor the dabigatran dose to improve the efficacy and safety of this drug.

Personalised treatment with coumarin derivatives

While the new oral anticoagulants will be used more widely, in some cases coumarin derivatives might still be preferred over the new oral anticoagulants. Physicians have more experience with coumarin derivatives and therefore might prefer to describe these 'old' drugs. Other physicians might prefer the new drugs, but prescribe coumarin derivatives to specific patients. This could be the case for patients with, for example, hepatic or renal impairment, patients with a higher risk for non-adherence or patients who prefer using coumarin anticoagulants instead of the new drugs because of the disadvantages of the new drugs. For these patients, personalised dosing of coumarin derivatives by using a pharmacogenetic-guided algorithm could be a good treatment option. Currently, more evidence on the benefit of genotyping is collected, which is expected in the near future.

If pharmacogenetic-guided dosing is proven to increase the effectiveness and safety of coumarin anticoagulant therapy, several issues should be addressed before it can be used on a large scale. First, someone will need to perform the genetic test. This can be the GP, a specialised physician, a nurse or the pharmacist, depending on the organisation of care in the relevant country. With the novel point-of-care test described earlier in this chapter it is not necessary to send a blood sample to a laboratory, which saves time. The point-of-care test is a very easy method which can also be performed by a nurse without laboratory training. However, if many patients will be genotyped it might be more efficient to genotype multiple samples

at the same time in a clinical chemistry laboratory. After performing the test, the results should be documented and made available to other involved persons, such as the physician and the pharmacist. The physician determining the starting dose should know how to interpret the results and how to calculate the required dose. All these issues require involvement of different stakeholders.

How pharmacogenetic-guided dosing can be implemented and how the workflow should be designed depends on the current organisation of care in the relevant country. In countries where anticoagulant clinics are involved, the role of these clinics will change considerably when coumarin derivatives will be used less frequently because of the increasing use of the new oral anticoagulants. The role of these clinics could then, for example, be concentrated more on patient education or advice to clinicians and pharmacists. This could include the more complicated issues with the new oral anticoagulants, such as reversal therapy, advice on pharmacogenetic issues with coumarin derivatives or maybe also on pharmacogenetic issues with the new oral anticoagulants, because pharmacogenetics might also play a role in the prescription of these new drugs [35].

Economic considerations

Because the quality of care and associated costs vary among different countries, the decision about which treatment option should be used can be different between countries. In some situations improving the quality of current care might be more attractive than using the new oral anticoagulants. This can be achieved in several ways, for example by setting up specialised anticoagulation clinics, using personalised medicine and pharmacogenetic-guided dosing or providing extra patient education to improve adherence. Because these options can also lead to increased costs, it is important to assess the cost-effectiveness of these options also. Cost-effectiveness studies are important to inform decision makers about the economic consequences of the different treatment options. The budget impact of the different options will also have to be considered, especially in an economic situation where further increases in healthcare costs are not feasible.

Future

More information on the effectiveness and cost-effectiveness of pharmacogenetics with coumarin derivatives can be expected in the near future. We expect to provide the results on the effectiveness of genotyping from the EU-PACT trial in the coming months and we will also use this data to assess the cost-effectiveness. For the different European countries there will be data on patient characteristics, such as the prevalence of variant genotypes, the number of INR measurements required in the intervention and control arm, baseline quality of life and of course the percentage time in range during the first 3 months of therapy for both the intervention and control arm. Much information from this thesis has been collected to be used in our cost-effectiveness analysis with the EU-PACT data. Many country specific parameters from chapter 10 will be used for the country specific cost-effectiveness analyses. These parameters include the characteristics of standard care,

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such as prevalence of coumarin anticoagulant use, frequency of INR measurements and setting, and country specific costs. Other information on, for example, disutility values of adverse events or outcome of events (fatal, disabilities etc.) will be derived from literature, as well as country specific guidelines on discount rates, perspective etc. The model with a link between data on percentage time in INR range and risk of adverse events described in chapter 9 of this thesis will serve as a basis for the model to investigate the cost-effectiveness using EU-PACT data. Cost-effectiveness analyses in different countries are possible when this model is combined with country specific parameters. This will make it possible to make reliable comparisons in the impact of pharmacogenetic-guided coumarin dosing between the different countries and to see in which countries it might be particularly cost-effective.

After the new oral anticoagulants have been used for several years and pharmacogenetic-guided dosing of coumarin anticoagulants has been implemented as well, it will be important to re-evaluate the effectiveness and cost-effectiveness of these treatment options in clinical practice, because they might differ from what is seen in clinical trials. This would be an interesting topic for future research.

Adherence issues would also be useful to investigate in the future. Little is known about the adherence to the new oral anticoagulants. When the adherence to the new oral anticoagulants is in reality lower than in the clinical trials, the benefit of these drugs might be lower. The beliefs about medication questionnaire could be used to look at the patient's attitude towards the new drugs and other methods, such as pill counts, could be used to assess therapy adherence. Another subject for future research might be to investigate how to improve adherence to anticoagulant drugs.

A final issue to consider in the future is the relationship between the explained variation in dose requirement and the possibility to maximise the effectiveness and safety of the treatment. With the current pharmacogenetic-guided algorithms, approximately 50% of the variation in dose requirement can be explained. It is unknown whether the risk of adverse events would further decrease if a larger percentage of the variation could be explained. Some patients require a very high or low dose, which cannot be explained by the *CYP2C9* and *VKORC1* polymorphisms or the other factors included in the algorithms. It is interesting to look at other factors explaining these discordant phenotypes. An analysis to identify novel variants in candidate genes determining sensitivity or resistance to anticoagulation is planned.

CONCLUSION

Personalised dosing of coumarin derivatives could be used to improve the therapy with coumarin derivatives in patients with atrial fibrillation, venous thromboembolism or other indications. Pharmacogenetic-guided algorithms can be used to predict the required coumarin dose before treatment initiation. However,

the impact of this strategy to improve anticoagulation control (and thereby increase the effectiveness and safety) seems to be limited to the first months of the treatment. New oral anticoagulants can also be used as alternatives to coumarin derivatives, because these drugs have been shown to be non-inferior or even superior to warfarin. For all treatment options, it is important to assess the cost-effectiveness in a country specific manner as quality of care and associated costs impact the cost-effectiveness considerably.

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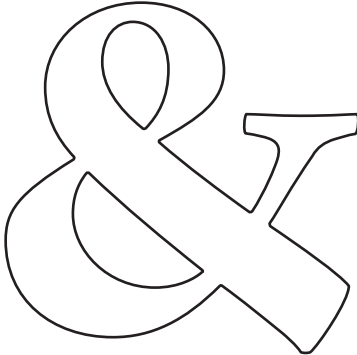
ADDENDUM

SUMMARY

Coumarin derivatives such as acenocoumarol, phenprocoumon and warfarin are frequently used for the prevention of stroke and systemic embolism in patients with atrial fibrillation or for the treatment of venous thromboembolism. These oral anticoagulants have a narrow therapeutic range and a large variability in dose requirement among patients. The anticoagulant effect is monitored by regular measurement of the International Normalised Ratio (INR). An INR below 2 is related to therapy failure and thereby leads to an increased risk of stroke or systemic embolism, while an INR above 3.5 leads to an increased risk of bleeding. Personalised dosing using genetic information is expected to help physicians to prescribe the required dose from the start of the therapy and thereby increase the efficacy and safety of the treatment. In the European Pharmacogenetics of Anticoagulant Therapy (EU-PACT) trial, we tested a dosing algorithm based on age, sex, height, weight, concomitant amiodarone use and *CYP2C9* and *VKORC1* genotypes. It is important to assess the cost-effectiveness of pharmacogenetic-guided coumarin dosing, because this information is used by payers such as health insurers to make decisions about reimbursement. In this thesis we describe the clinical and economic issues of personalised treatment with oral anticoagulant drugs.

In **Chapter 1** we provide a general introduction and describe the aims of this thesis. Our aim was to study genetic and other determinants that explain the variability in response to coumarin derivatives. We also aimed to study the economic consequences of different options (personalised medicine or using new oral anticoagulant drugs) to improve anticoagulant therapy. More background information is provided in **Chapter 2**. Currently, patients initiating coumarin anticoagulant therapy receive a standard loading dose for the first few days. The dose is adjusted when the INR is measured after a few days. When patients have reached a stable INR in the therapeutic range and a stable dose, INR measurements will be repeated every 4-6 weeks. The stable dose can vary up to 10-fold between patients. Polymorphisms in the *CYP2C9* gene, coding for the main metabolising enzyme of coumarin anticoagulants, and the *VKORC1* gene, coding for the target enzyme of coumarin anticoagulants, together explain approximately one-third of the variation in dose requirement. Many genotype-guided dosing algorithms for warfarin have been developed in different populations. In contrast, fewer algorithms have been published for acenocoumarol and phenprocoumon. With these algorithms, more than 50% of dose variation can be explained. Several clinical studies have been published describing the effect of pharmacogenetic-guided dosing on anticoagulation control, but no convincing evidence about the clinical significance exists yet. Currently ongoing large randomised trials such as EU-PACT are expected to provide this evidence and this information can then also be used to assess the cost-effectiveness of pharmacogenetic-guided dosing.

Different determinants of variation in response to coumarin anticoagulants

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are studied in **Part I** of this thesis. We described the association between polymorphisms in *CYP2C9* and *VKORC1* and over- and under-anticoagulation in different time periods after treatment initiation in **Chapter 3**. *VKORC1* genotype had the largest influence on over- or under-anticoagulation. Among wild-type patients, 73% of the patients had a subtherapeutic INR and 30% a supratherapeutic INR in the first month, compared to 45% with a subtherapeutic INR and 74% with a supratherapeutic INR among patients carrying two variant alleles. After the first month, the differences were much smaller and no difference was seen after the sixth month. In **Chapter 4** we performed similar analysis for phenprocoumon and found no differences in risk of over- or under-anticoagulation between the genotypes after the first month. Pharmacogenetic information could therefore be used to prevent subtherapeutic or supratherapeutic INRs in the first month, but not after the first month for phenprocoumon or after 3-6 months for acenocoumarol.

Concomitant medication use can also influence the required coumarin dose. In **Chapter 5** we investigated the interaction between the proton pump inhibitors omeprazole and esomeprazole and phenprocoumon. On average, patients using omeprazole or esomeprazole required a dose that was 0.49 or 0.39 mg per day lower than non-users respectively. When these proton pump inhibitors were included in a genotype-guided dosing algorithm, 56.7% of the dose variation could be explained, which is only marginally higher than an algorithm not

including proton pump inhibitors. Next to prescribing the correct dose to a patient, it is important that a patient is compliant with this dose. Therapy adherence is associated with the beliefs that patients have about their medicines. We described the beliefs that patients included in the EU-PACT trial have about acenocoumarol and phenprocoumon in **Chapter 6**. On average, coumarin users had a positive attitude towards their treatment. The beliefs score about the necessity of the treatment was higher than the beliefs score about the concerns (for example about side effects). This was not different from users of other cardiovascular drugs. However, patients with atrial fibrillation did have a lower score on the necessity beliefs than patients with venous thromboembolisms. Because of this less positive attitude, the risk of non-adherence is higher in patients with atrial fibrillation than in patients with venous thromboembolism.

In **Part II** of this thesis we described studies on the cost-effectiveness of pharmacogenetic-guided dosing of coumarin derivatives, as well as the cost-effectiveness of the new oral anticoagulants dabigatran, apixaban and rivaroxaban. We provide an overview of cost-effectiveness studies on pharmacogenetic-guided dosing of coumarin derivatives published up to the end of 2009 in **Chapter 7**. All studies focused on genotype-guided dosing of warfarin in the United States, except one study on acenocoumarol in The Netherlands. The results of these studies varied considerably. In most studies genotyping led to improved health outcomes, but the costs were also higher than for standard care, with an incremental cost-effectiveness ratio up to

almost 350,000 US$ per Quality-Adjusted Life-Year (QALY) gained. The wide variation in results made it impossible to conclude whether or not pharmacogenetic-guided dosing is a cost-effective strategy. More evidence on the effectiveness of genotyping on anticoagulation control was required and the costs of the genetic test needed to be defined more precisely.

In **Chapter 8** we evaluated a study by Meckley *et al.* on the benefits, risks and costs of pharmacogenetic-guided dosing of warfarin, published in 2010. In this study, the probabilities to experience a haemorrhagic or thromboembolic event were based on the time spent in different INR ranges. The percentage time spent in these ranges was derived from a clinical trial (CoumaGen) published in 2007. The incremental cost-effectiveness ratio of genotype-guided dosing versus standard care was US$60,000 per QALY gained, but the sensitivity analyses showed large uncertainty because the effectiveness of genotyping in clinical practice is still unclear. The model was adapted to study the cost-effectiveness of pharmacogenetic-guided phenprocoumon dosing in The Netherlands in **Chapter 9**. In 2012, the results of the CoumaGenII trial were published, which showed a larger effect of genotyping than the CoumaGen trial published in 2007. We used data on the percentage time spent in the different INR ranges from this trial and assumed that genotyping one patient using a point-of-care genetic test would cost €40. Pharmacogenetic-guided dosing increased the QALYs only by 0.0057 (2 days in full health), but the incremental costs were also low (€15). The incremental cost-

effectiveness ratio was €2658. Because there was still a large uncertainty regarding the effectiveness, this study could not provide enough evidence to conclude whether or not pharmacogenetic-guided dosing should be implemented.

The management and costs of anticoagulant care can influence the cost-effectiveness of pharmacogenetic-guided coumarin dosing. We described the organization and costs of anticoagulant care for the treatment of atrial fibrillation in 6 European countries in **Chapter 10**. The setting in which the management of the treatment took place varied from a specialised anticoagulation clinic to the general practitioner and hospital settings. The percentage time spent in the target range, which is a measure for quality of anticoagulation, also varied considerably between the countries. The highest percentage time within range was seen in The Netherlands, which uses a system of specialised anticoagulation clinics. Because of these differences and the differences in costs associated with coumarin therapy and management of complications, it is likely that the cost-effectiveness of pharmacogenetic-guided dosing will also vary appreciably among countries. It is therefore important to perform country specific cost-effectiveness analyses. In **Chapter 11** we conducted country specific cost-effectiveness analyses on the new oral anticoagulants (NOACs) versus coumarin derivatives in The Netherlands and in the United Kingdom. In The Netherlands, acenocoumarol is most frequently used and treatment is monitored and guided by specialised anticoagulation clinics with a percentage time spent in the therapeutic

range of 76-79%. In The United Kingdom, warfarin is most frequently used and many patients are treated by a general practitioner with a percentage time spent in the therapeutic range of approximately 63%. Because of these differences, the incremental cost-effectiveness ratios of the NOACs were higher in The Netherlands than in the United Kingdom, although dabigatran and apixaban could be considered cost-effective in both countries. The incremental cost-effectiveness ratio of rivaroxaban versus acenocoumarol in The Netherlands was almost €33,000 per QALY gained and this drug was therefore not considered as cost-effective in this country.

In **Chapter 12** we discuss the findings described in this thesis and their relevance, including the strengths and limitations of the studies, implications for clinical practise and future research. Pharmacogenetic-guided dosing of coumarin derivatives could be used to improve the therapy for patients with atrial fibrillation or venous thromboembolism. NOACs were also shown to be promising alternatives to coumarin derivatives. The results of the cost-effectiveness studies in this thesis underline the importance of country specific cost-effectiveness analysis when looking at the economic consequences of improving oral anticoagulant therapy.

SAMENVATTING

Acenocoumarol, fenprocoumon en warfarine zijn veel gebruikte orale antistollingsmiddelen voor het voorkomen van stolsels en bijvoorbeeld een herseninfarct bij patiënten met atrium fibrilleren of voor de behandeling van veneuze trombose. Deze antistollingsmiddelen behoren tot de groep van cumarinederivaten en hebben een kleine therapeutische breedte. Ook bestaat er een grote variabiliteit in de benodigde dosering onder patiënten. Het antistollingseffect wordt regelmatig gecontroleerd door het meten van de INR (International Normalised ratio). Wanneer een patiënt een INR lager dan 2 heeft, is er sprake van onderbehandeling en bestaat er een verhoogde kans op een herseninfarct of het ontstaan van een stolsel elders in de bloedsomloop. Bij een INR hoger dan 3,5 wordt het risico op een bloeding groter. Het berekenen van een persoonlijke dosering kan artsen helpen om gelijk vanaf het begin van de behandeling de juiste hoeveelheid antistollingsmiddel voor te schrijven. Er wordt verwacht dat hierdoor de effectiviteit en veiligheid van de behandeling verbeterd kunnen worden. In het EU-PACT (European Pharmacogenetics of Anticoagulant Therapy) onderzoek hebben wij een doseer algoritme op basis van leeftijd, geslacht, lengte, gewicht, amiodaron gebruik en *CYP2C9* en *VKORC1* genotype getest. Het is belangrijk om de kosteneffectiviteit van doseren op basis van het genotype te onderzoeken, omdat deze informatie gebruikt wordt om bijvoorbeeld te bepalen of de genetische test vergoed zou moeten worden door de zorgverzekeraar. In dit proefschrift beschrijven we de klinische en economische gevolgen van een geïndividualiseerde behandeling met orale antistollingsmiddelen.

In **Hoofdstuk 1** geven we een algemene introductie op het onderwerp en beschrijven we het doel van het proefschrift. Het doel was om zowel genetische als andere factoren te onderzoeken die van invloed zijn op de variabiliteit in de reactie op cumarinederivaten. Daarnaast hebben we de kosteneffectiviteit van verschillende opties voor het verbeteren van de antistollingsbehandeling (gepersonaliseerd doseren of nieuwe orale antistollingsmiddelen zoals dabigatran, apixaban of rivaroxaban) bestudeerd. Meer achtergrond informatie wordt gegeven in **Hoofdstuk 2**. De standaard antistollingszorg houdt op dit moment in dat patiënten die starten met een cumarinederivaat eerst een standaard oplaaddosering voorgeschreven krijgen. Na een paar dagen wordt de INR gemeten en de dosering aangepast. Ook wanneer de INR binnen het therapeutisch gebied ligt en de patiënt een stabiele dosering heeft, wordt de INR nog ongeveer elke 4-6 weken gemeten. De stabiele dosering kan wel tot een factor 10 verschillen tussen patiënten. Ongeveer één derde van deze variatie kan worden verklaard door genetische verschillen in twee genen. Het *CYP2C9* gen codeert voor het belangrijkste enzym in het metabolisme van cumarinederivaten. Het *VKORC1* gen codeert voor het aangrijpingspunt van deze antistollingsmiddelen. In de literatuur zijn al vele doseeralgoritmes voor warfarine op basis van deze genetische informatie in verschillende populaties beschreven. Voor acenocoumarol en fenprocoumon zijn ook een aantal algoritmes ontwikkeld, hoewel dit er minder zijn dan voor warfarine.

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Met behulp van deze algoritmes kan meer dan 50% van de variabiliteit in benodigde dosering worden verklaard. Het effect van deze doseeralgoritmes op de effectiviteit en veiligheid van de antistollingsbehandeling is al in een aantal klinische studies onderzocht, maar er bestaat nog geen overtuigend bewijs over de klinische relevantie van de genetische test. Op dit moment zijn er nog een aantal grote studies gaande, waaronder EU-PACT, die meer bewijs zullen leveren. Deze informatie kan ook gebruikt worden om de kosteneffectiviteit van dosering op basis van het genotype te bepalen.

In **Deel I** van dit proefschrift zijn verschillende factoren bestudeerd die invloed kunnen hebben op de variatie in reactie op de antistollingsmiddelen. De associatie tussen genetische verschillen in *CYP2C9* en *VKORC1* en INR uitschieters in verschillende perioden na het starten van de behandeling is beschreven in **Hoofdstuk 3**. *VKORC1* genotype was het sterkst geassocieerd met het wel of niet hebben van INR uitschieters. Van de wild-type patiënten had 73% een INR lager dan 2 en 30% een INR hoger dan 3,5 in de eerste maand. Onder de patiënten met twee variant allelen had daarentegen maar 30% een INR lager dan 2 en wel 74% een INR hoger dan 3,5. Deze verschillen waren veel kleiner na de eerste maand en niet meer aanwezig vanaf de zesde maand. In **Hoofdstuk 4** hebben we deze analyses herhaald voor fenprocoumon. Bij fenprocoumon waren er geen verschillen in het risico op een te hoge of te lage INR tussen de genotypen na de eerste maand van de behandeling. Farmacogenetica kan gebruikt worden om het risico op onder- of overdosering te verkleinen, maar dit is beperkt tot de eerste maand voor fenprocoumon en tot de eerste drie tot zes maanden voor acenocoumarol.

Gelijktijdig gebruik van andere geneesmiddelen heeft ook invloed op de benodigde dosering. In **Hoofdstuk 5** hebben we de interactie tussen de protonpompremmers omeprazol en esomeprazol en fenprocoumon onderzocht. Gebruikers van omeprazol of esomeprazol hadden gemiddeld respectievelijk een 0,49 en 0,39 mg/dag lagere dosering nodig in vergelijking met patiënten die deze middelen niet gebruikten. Door het gebruik van protonpompremmers op te nemen in een doseeralgoritme waarbij ook gebruik gemaakt wordt van de genetische informatie, kon 56,7% van de variatie verklaard worden. Met hetzelfde doseeralgoritme zonder protonpompremmers, kon 55,9% verklaard worden. Naast het voorschrijven van de juiste dosering is het ook belangrijk dat de patiënt zich aan de voorgeschreven dosering houdt. Therapietrouw is geassocieerd met de opvattingen die patiënten kunnen hebben over hun geneesmiddelen. In **Hoofdstuk 6** hebben we de opvattingen over fenprocoumon en acenocoumarol beschreven van patiënten uit de EU-PACT studie. Over het algemeen hadden cumarine gebruikers een positieve houding ten opzichte van hun behandeling. De score over de noodzaak van het gebruik van het antistollingsmiddel was hoger dan de score over de zorgen over bijvoorbeeld bijwerkingen. Dit was ook het geval bij gebruikers van andere middelen voor hart- en vaatziekten. Patiënten die een cumarinederivaat gebruikten voor atriumfibrilleren scoorden wel lager op de noodzaak opvattingen dan patiënten die

het voor veneuze trombose gebruikten. Door deze minder positieve houding ten opzichte van de antistollingsbehandeling, is het risico op therapie-ontrouw hoger bij patiënten met atriumfibrilleren dan bij patiënten met veneuze trombose.

In **Deel II** van dit proefschrift hebben we studies naar de kosteneffectiviteit van doseren op basis van het genotype en van de nieuwe antistollingsmiddelen dabigatran, apixaban en rivaroxaban beschreven. We geven een overzicht van alle tot eind 2009 gepubliceerde kosteneffectiviteitsstudies naar genotyperen voor de start van de cumarine behandeling in **Hoofdstuk 7**. Al deze studies, behalve één, keken naar het bepalen van de warfarine dosering op basis van het genotype in de Verenigde Staten. Er was één studie naar de acenocoumarol dosering in Nederland. De resultaten van de studies lagen ver uiteen. In de meeste studies leverde het doseren op basis van het genotype wel een gezondheidswinst op, maar ook de kosten waren hoger dan voor de huidige standaard zorg. De kosten per voor kwaliteit van leven gecorrigeerd levensjaar (QALY) was in één studie zelfs $350.000. Omdat de resultaten zo ver uiteen lagen, was het niet mogelijk om te concluderen of het vooraf genetisch testen kosteneffectief is of niet. Er is meer bewijs nodig over de effectiviteit en veiligheid van genetische doseeralgoritmen bij de cumarine behandeling en ook de kosten van de genetische test moeten preciezer worden vastgesteld.

In **Hoofdstuk 8** hebben we een onderzoek van Meckley en collega's beoordeeld. Dit onderzoek naar de gezondheidswinst en de kosteneffectiviteit van genotyperen voor de warfarine behandeling is gepubliceerd in 2010. De kans op bloedingen of trombose was gebaseerd op het percentage tijd binnen verschillende INR grenswaarden. Voor deze percentages maakten de onderzoekers gebruik van gegevens uit een klinische studie (CoumaGen) gepubliceerd in 2007. Ten opzichte van standaard zorg waren de extra kosten per gewonnen QALY in deze studie $60.000, maar er bleek nog een grote onzekerheid te zijn in de sensitiviteitsanalyse, met name over het effect van genotyperen in de klinische praktijk. Het model van Meckley en collega's hebben wij in **Hoofdstuk 9** aangepast om de kosteneffectiviteit van genotyperen bij de fenprocoumon behandeling in Nederland te onderzoeken. In 2012 zijn de resultaten van de CoumaGenII trial gepubliceerd. In dit onderzoek werd een groter effect van genotyperen gezien dan in de CoumaGen trial van 2007. Wij hebben gebruik gemaakt van het percentage tijd in het INR streefgebied uit de nieuwste studie. Daarnaast hebben we aangenomen dat de patiënten konden worden gegenotypeerd met een point-of-care test voor €40 per patiënt. Door patiënten voor de start met fenprocoumon te genotyperen kon er een geringe gezondheidswinst van 0,0057 QALYs behaald worden (2 dagen in volledige gezondheid) bij een kleine toename in kosten (€15). De kosteneffectiviteitsratio was €2658 per gewonnen QALY. Vanwege de nog steeds bestaande onzekerheid over de effectiviteit van genotyperen, konden we met deze studie nog niet genoeg bewijs leveren om te concluderen of doseren op basis van het genotype zou moeten worden geïmplementeerd.

De organisatie en de kosten van de antistollingszorg kunnen de kosteneffectiviteit van doseren op basis van het genotype

beïnvloeden. In **Hoofdstuk 10** hebben we de organisatie van de antistollingszorg en de gerelateerde kosten voor de behandeling van atriumfibrilleren in zes Europese landen beschreven. In sommige landen wordt de behandeling met cumarinederivaten begeleid door gespecialiseerde trombosediensten, terwijl dit in andere landen gedaan wordt door de huisarts of een arts in het ziekenhuis. Het percentage tijd binnen de INR streefwaarden (een maat voor de kwaliteit van de antistollingsbehandeling) verschilt ook tussen de landen. In Nederland, waar patiënten worden behandeld in trombosediensten, was dit percentage het hoogst. Door deze verschillen en door verschillen in de kosten gerelateerd aan de cumarine behandeling of de behandeling van complicaties, zal ook de kosteneffectiviteit van genotyperen in de verschillende landen uiteenlopen. Daarom is het belangrijk om land-specifieke kosteneffectiviteitsanalyses uit te voeren. In **Hoofdstuk 11** hebben wij een land-specifieke kosteneffectiviteitsanalyse uitgevoerd waarin we de nieuwe antistollingsmiddelen dabigatran, apixaban en rivaroxaban vergeleken met de cumarinederivaten in Engeland en in Nederland. In Nederland is acenocoumarol het meest gebruikte cumarinederivaat en is het percentage tijd in het INR streefgebied in de trombosediensten 76-79%. In Engeland wordt warfarine het meest gebruikt en de meeste patiënten

worden door de huisarts behandeld. Het percentage tijd binnen het INR streefgebied is daar ongeveer 63%. Door deze verschillen waren de kosten per gewonnen QALY bij de nieuwe antistollingsmiddelen lager in Engeland dan in Nederland. In beide landen kon de behandeling met dabigatran en apixaban gezien worden als kosteneffectief. In Nederland waren de extra kosten van rivaroxaban bijna €33.000 per gewonnen QALY en daarom kon dit middel als niet kosteneffectief worden beschouwd in dit land.

In **Hoofdstuk 12** bespreken we de resultaten van dit proefschrift en de relevantie ervan. Daarbij beschrijven we ook de plus- en minpunten van de studies, de implicaties voor de klinische praktijk en aanbevelingen voor toekomstig onderzoek. Het bepalen van de cumarine dosering op basis van het genotype kan de behandeling van patiënten met atriumfibrilleren of veneuze trombose verbeteren. Daarnaast zijn ook de nieuwe antistollingsmiddelen veelbelovende alternatieven voor cumarinederivaten. Uit de resultaten van de kosteneffectiviteitsstudies in dit proefschrift blijkt dat het van belang is om land-specifieke kosteneffectiviteitsanalyses uit te voeren als er gekeken moet worden naar de economische gevolgen van het verbeteren van de antistollingsbehandeling.

DANKWOORD

Daar is ie dan, mijn eigen proefschrift! Het voelt heerlijk om het nu af te hebben, na 4 jaar lang hard werken. Maar helemaal alleen heb ik het natuurlijk niet gedaan. Ik weet dat God mij veel heeft gegeven om dit mogelijk te maken. Daarnaast zijn er veel mensen om mij heen die ik graag wil bedanken voor hun bijdrage.

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