A Randomised Comparison of the Quality of anticoagulant therapy with Two Vitamin K antagonists: Warfarin versus Phenprocoumon

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Abstract

Context Several studies have compared different vitamin K antagonists with regard to the quality of treatment, e.g. stability. The results were mostly, but not always, in favour of the longer acting vitamin K antagonists. Only one randomised study compared warfarin and phenprocoumon.

Objective The aim of our study was to investigate whether oral anticoagulant treatment with warfarin leads to a more or less stable anticoagulant status than is achieved with phenprocoumon.

Methods We conducted a randomised controlled trial among patients with an indication for anticoagulant treatment at the Leiden Anticoagulation Clinic. We included patients who initiated oral anticoagulant therapy and patients who were already using a different vitamin K antagonist (acenocoumarol), and who were switched. We compared an oral anticoagulant treatment with warfarin with a treatment with phenprocoumon. Follow-up was 6 months. The primary outcome measure was the percentage of time spent in therapeutic range.

Results From March 1st 2004 to January 2008, 312 patients finished the follow period and were included in this analysis. One patient died before the first INR measurement. The median time spent in the therapeutic range was 74.7% (IQR 58.8-87.0). Thirty eight percent of patients spent more than 80% of the time in therapeutic range. There was no difference in time spent in the therapeutic range between men and women, and between patients who initiated oral anticoagulant treatment and patients who switched from acenocoumarol. The median time between two visits was 11.7 days (IQR 10.0 – 13.9).

Trial registration The trial is registered in the ISRCTN register with identifier ISRCTN60446748. (www.controlled-trial.org)
**Introduction**

Coumarins are among the most frequently used drugs worldwide and the number of indications for which they are prescribed is still growing. Worldwide there are different vitamin K antagonists available. There are three different types most frequently used: acenocoumarol, warfarin and phenprocoumon. These vitamin K antagonists mainly differ in half-life: Acenocoumarol has the shortest half-life of 11 hours, followed by warfarin with 36-42 hours and the longest half-life is seen in phenprocoumon with approximately 140 hours [1-4]. The clearance of these coumarins also is dissimilar. Acenocoumarol is for its elimination completely dependent on hydroxylation by cytochrome p450 (CYP). Warfarin is also dependent on reduction processes [5]. Phenprocoumon can, in addition to elimination as hydroxylated metabolites, be eliminated as parent compound and is thus less dependent on hydroxylation by CYP. These differences in dependence on hydroxylation by the CYP enzymes offer an explanation of different responses found in studies investigating the effects of polymorphisms in the CYP2C9 gene on clearance of specific coumarin classes [6,7]. Several studies have compared these different vitamin K antagonists with regard to the quality of treatment, e.g. stability. Most studies have compared the short acting acenocoumarol to the longer acting warfarin or phenprocoumon. The results were mostly, but not always, in favour of the longer acting vitamin K antagonists. [8-16]. Only one randomised comparison between warfarin and phenprocoumon was made by Rodman *et al.* in 1964 [15]. In their comparative study they evaluated 4 different anticoagulants: phenprocoumon, bishydroxycoumarin, diphenadione and warfarin. They concluded that phenprocoumon appeared to be superior to the other anticoagulants in terms of ease of maintenance therapy, although all others were also satisfactory for clinical use.
The aim of our study was to investigate whether oral anticoagulant treatment with warfarin leads to a more stable oral anticoagulant treatment than is achieved with phenprocoumon. In this report we will discuss the design of the study and give general results regarding the quality of oral anticoagulant treatment of the participating patients.

**Methods**

**Study design**

We performed a randomised controlled trial comparing two groups: patients receiving oral anticoagulant treatment with phenprocoumon and patients using warfarin. We used block randomisation stratified for the centre a patient was referred from to assure an equal number of patients on both anticoagulants among patients from each centre. The study was not blinded since dosing of warfarin and phenprocoumon has to be done in different ways due to the difference in half life. For safety reasons, it is also necessary that patients and physicians are aware of which vitamin K antagonists they are taking.

The study was conducted at the Leiden Anticoagulation Clinic in the Netherlands. At this anticoagulation clinic most patients are treated with phenprocoumon (approximately 80%), all other patients are treated with acenocoumarol. Warfarin is not registered for use in the Netherlands.

**Patients**

Recruitment of patients occurred from March 1st 2004 and is ongoing. Two patient groups were included in the trial. The first group consisted of patients initiating oral anticoagulant treatment and was recruited from three hospitals, all in the greater Leiden area, i.e., the departments of Cardiology and Internal Medicine of the Leiden University Medical Center, Diaconessenhuis Leiden, and Rijnland
Patient eligibility criteria for the first group were as follows: patients were eligible to participate when they were aged between 18 and 85 years and had an indication for anticoagulant treatment which required treatment for at least three months. Exclusion criteria were pregnancy or intended pregnancy, renal dialysis, chemotherapy, known allergic reactions to warfarin or phenprocoumon or a contra-indication to oral anticoagulant treatment. Only patients who lived in the working area of the Leiden Anticoagulation clinic could participate in the study. Patients were randomised to a treatment with either phenprocoumon or warfarin and were followed until end of treatment or, when the indication required the treatment to continue over 6 months, follow-up ended at 6 months.

The second group included in this trial consisted of patients already using acenocoumarol and who were recruited at the Anticoagulation clinics of Leiden and The Hague. We chose patients using acenocoumarol so that for the study participants always had to switch to a treatment with another vitamin K antagonist, and there was no possibility of attrition of susceptibles specific to phenprocoumon. Patients were eligible to participate when they were aged between 18 and 85 years and had an indication for long term anticoagulant treatment. For this group the same exclusion criteria were applied as was for the first group. After written informed consent they were randomized and switched to a treatment with either phenprocoumon or warfarin and follow-up was again 6 months.

All patients participating in the trial were part of the routine care in the Anticoagulation clinic. We obtained approval from Medical Ethics Review Committee of the Leiden University Medical Center before start of the study and all patients gave written informed consent before randomization. The trial is registered in the ISRCTN register with identifier ISRCTN60446748 (http://www.controlled-trials.com).
Analyses

We analysed all patients treated at the Leiden Anticoagulation clinic who finished the follow-up period at January 1\textsuperscript{st} 2008. The primary outcome measure was quality of anticoagulant therapy, which was defined as the mean percentage of time spent in the therapeutic range. We used the linear interpolation method to determine this quantitative measure of quality of anticoagulant therapy [17]. Therapeutic ranges were as they were applied in our routine anticoagulant practice: an INR between 2.0 and 3.5 for most indications (i.e. venous thrombosis, atrial fibrillation) and between 2.5 and 4.0 for patients needing a high intensity of anticoagulation (e.g. patients with prosthetic heart valves). In case a patient had less than 2 INR measurements in total, no time in therapeutic range was calculated, and the patient was excluded. When the time between two INR measurements exceeded 9 weeks, no time in therapeutic range was calculated for this period, and this period was excluded.

Secondary outcome measures were the median time between visits, the time above and below the therapeutic range and the time needed to achieve an INR within range after start of treatment. Bleeding complications were classified as major when they were fatal or necessitated hospitalisation. Minor bleeding complications were all other bleeding events, in which ecchymoses were only counted when more than 10 cm in diameter and epistaxis only when the duration exceeded 30 minutes.

Statistical Analyses

All outcomes are shown as means or percentages with the corresponding 95\% confidence interval of the difference based on t or binomial distributions or
medians with the corresponding interquartile range (IQR). All calculations were performed using the statistical package SPSS version 14.0 (SPSS Inc, Chicago, Ill).

**Results**

From March 1\textsuperscript{st} 2004 to January 2008, 405 patients were included of whom 312 patients finished the study. One patient dropped out, while 75 had not completed the 6 months study duration. Of the 312 patients, 162 were randomised to the warfarin group and 150 to the phenprocoumon group. The study population consisted of 218 patients who initiated an oral anticoagulant therapy (112 warfarin group, 106 phenprocoumon group) and 94 patients who were already treated with oral anticoagulants (of whom 50 were switched to warfarin, and 44 to phenprocoumon).

![Figure 1. Enrollment, Randomisation and Data Analysis](image)
One patient discontinued the treatment before the first INR measurement because of a bleeding complication (phenprocoumon group). The total follow up time was 119.3 person years, 63.2 person years in the warfarin group and 56.1 person years in the phenprocoumon group. Seventy five patients had a follow up shorter than 6 months for various reasons. Two patients stopped the treatment because of treatment-related complications (1 warfarin group, 1 phenprocoumon group) and 1 patient died of unknown cause (phenprocoumon group). Figure 1 summarises enrolment, randomisation, follow up and analysis of all patients.

Baseline characteristics are shown in table 1. There were more men than women (201 (62.2%) women versus 111 men (34.4%)), equally divided over the two treatment groups. Median age was 66 years (IQR 58-73). The majority of patients started with oral anticoagulants because of atrial fibrillation or venous thrombosis. Almost all patients had a target intensity of INR 2.5 – 3.5. Demographic characteristics, indication for oral anticoagulant treatment, and target intensity of anticoagulation did not differ between the two groups.

<table>
<thead>
<tr>
<th>Table 1. Patient characteristics</th>
<th>Patients treated with warfarin (n=162)</th>
<th>Patients treated with phenprocoumon (n=149)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (IQR)</td>
<td>64.1 (59-73)</td>
<td>63.3 (56-74)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men (n, %)</td>
<td>110 (67.9)</td>
<td>91 (61.1)</td>
</tr>
<tr>
<td><strong>Indication</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial Fibrillation (n, %)</td>
<td>79 (48.8)</td>
<td>70 (47.0)</td>
</tr>
<tr>
<td>Venous thrombosis (n, %)</td>
<td>31 (19.1)</td>
<td>25 (16.8)</td>
</tr>
<tr>
<td>Heart valve prosthesis (n, %)</td>
<td>9 (5.6)</td>
<td>9 (6.0)</td>
</tr>
<tr>
<td>Other cardiac indication (n, %)</td>
<td>9 (5.6)</td>
<td>9 (6.0)</td>
</tr>
<tr>
<td>Prophylactic (n, %)</td>
<td>32 (19.8)</td>
<td>32 (21.5)</td>
</tr>
<tr>
<td>other (n, %)</td>
<td>2 (1.2)</td>
<td>4 (2.7)</td>
</tr>
<tr>
<td><strong>Intensity (target)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (2.5 – 3.5) (n, %)</td>
<td>144 (88.9)</td>
<td>129 (86.6)</td>
</tr>
<tr>
<td>High (3.0 – 4.0) (n, %)</td>
<td>15 (9.3)</td>
<td>20 (13.4)</td>
</tr>
<tr>
<td>Switched (n, %)</td>
<td>3 (1.8)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td><strong>Group</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initiating oral anticoagulant treatment</td>
<td>112 (69.1)</td>
<td>105 (70.5)</td>
</tr>
<tr>
<td>Switched from acenocoumarol</td>
<td>50 (30.9)</td>
<td>44 (29.5)</td>
</tr>
</tbody>
</table>
The median time spent within the therapeutic range was 74.7% (interquartile range (IQR) 58.8-87.0). Patients who switched from acenocoumarol to warfarin or phenprocoumon spent an equal amount of time in the therapeutic range as patients initiating treatment (75.8% versus 73.4%). There was no difference in time in therapeutic range between men and women (74.5% versus 75.1%). One hundred and nineteen patients (38.1%) spent more than 80% of the time within their therapeutic range, 228 (73.1%) spent more than 60% of time in range (figure 2).

![Figure 2](image.png)

**Figure 2.** Percentage of time spent within therapeutic range.

Time between two visits is shown in figure 3. Overall, the median time between two visits was 11.7 days (IQR 10.0 – 13.9), with 59.2% of patients with a median time between two visits between 10 and 15 days.
Discussion

In this study we described the study design of our trial of which the primary aim is to compare the quality of a treatment with warfarin to the quality of a treatment with phenprocoumon. In addition we gave an overview of the overall quality of anticoagulant treatment, without giving the results for the two treatment groups separately since the trial is ongoing. The overall quality of anticoagulant treatment was high, with a median time spent within the therapeutic range of 74.7% (IQR 58.8-87.0).

This study has several potential limitations. Firstly, in our anticoagulation clinic the majority of patients is treated with phenprocoumon. This may potentially bias the present comparison between anticoagulant treatment with phenprocoumon versus warfarin, since the physicians dosing the patients are experienced in dosing phenprocoumon, but inexperienced in dosing warfarin. We will investigate this phenomenon with an analysis in which we compare patients randomised to a
treatment with warfarin in the beginning of the trial to patients randomised to warfarin at the end of the trial to see whether there was a large learning effect in warfarin dosing among the physicians.

Secondly, this study was not blinded. Blinding of trials was introduced to ensure random allocation, to avoid selective drop-outs, to avoid differential co-treatment, and to avoid bias in the assessment of the outcome measures. It is believed that randomised controlled trials are optimally valid when patients as well as physicians or investigators are blinded for which treatment a patient is allocated to. In trials comparing vitamin K antagonists however, it is not possible without extended sham procedures to blind patients and physicians since the half life of the vitamin K antagonist is needed to determine the dosage optimally. We believe that at the level of the patient we did not introduce any bias as result of the non-blindness of the trial. The outcome measure of this trial was the time spent in therapeutic range, i.e. the achieved INR. It is not likely that the patients’ knowledge about the vitamin K antagonist he or she is taking is of any influence on the measured INR. It could in theory affect a patients’ compliance to the treatment, but we do not have any reason to believe that the compliance will be different among the two groups. The knowledge of the physician to which treatment a patient is allocated to can be of influence on the time spent in therapeutic range. For example, a physician may be more cautious in one of the two treatment groups which would result in a shorter time between two INR measurements and less rigorous dosage changes. This would be evident in the data as a shorter time between two INR measurements in the group with the highest proportion of time spent in the therapeutic range.

The patients included in our trial are all out-patients, and therefore represent a selection of all patients treated with vitamin K antagonists with a relatively high health status, since a relevant proportion of patients treated with
vitamin K antagonists will be in-patients. Because this is a randomized trial this will not affect the validity of the results. In-patients are more likely to receive multiple and interacting medications and are more likely to have co morbidities. One may question therefore whether the results can be generalised to the total population of patients using vitamin K antagonists though there is no reason to assume this would not be the case.
References


