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Comparison of dosing algorithms for acenocoumarol and phenprocoumon using clinical factors with the standard care in the Netherlands

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ABSTRACT

Background: It has not been investigated how much the use of clinical factors in a dosing algorithm improves the percentage of time in therapeutic range (TTR). The present study aimed to compare the effect of dosing algorithms for acenocoumarol and phenprocoumon including clinical patient characteristics with standard care in the Netherlands.

Setting: The pre-EU-PACT study, an observational study in the Netherlands, was used to obtain standard care data. Data from the Dutch patients in the EU-PACT trial (comparing the use of a clinical algorithm with and without genetic information) was used for the clinical dosing algorithm.

Methods: For both acenocoumarol and phenprocoumon, the percentage of time in, below and above therapeutic International Normalized Ratio (INR) range during 12 weeks after treatment initiation were assessed in both studies.

Results: During the weeks 2-12, the clinical dosing algorithm of acenocoumarol (80 patients) led to a higher TTR (74.3% versus 68.0% in range 2.0-3.5, 95% Confidence interval [CI] difference: 0.5% to 11.8%), and a reduced percentage of time below INR 2 and above INR 3.5, compared with standard care (272 patients). For phenprocoumon, compared with standard care (484 patients), 80 patients treated by the dosing algorithm did not obtained a significantly higher TTR in range 2.0-3.5 or a lower percentage of time above 3.5, however, they spent more time with INR below 2.

Conclusion: The use of a clinical dosing algorithm for acenocoumarol seemed to improve the quality of anticoagulation therapy during the treatment of initial 2-12 weeks. For phenprocoumon, there was no statistically difference in anticoagulation control.

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Introduction

Vitamin K antagonists (VKA) or coumarin derivatives, such as warfarin, acenocoumarol and phenprocoumon are effective for the treatment and prevention of thromboembolic disease [1]. However, their use is challenging due to the narrow therapeutic window and high inter- and intra-individual variability in dose response. Therefore the international normalized ratio (INR), a measurement of anticoagulation activity is regularly measured, and used to guide dosing of these drugs. To improve the management of oral anticoagulant treatment, several computerized algorithms have been developed to assist physicians with their dosing decisions and using these has been shown to be superior to traditional dosing [2–4]. In the Netherlands, the use of similar computerized algorithms (eg. TRODIS, TDAS) are considered standard care in the anticoagulation clinics [5,6].

The dosage of coumarin anticoagulant agents needed by an individual patient is influenced by several factors, including age [7], sex, height, weight [8], concurrent drug therapy [9], vitamin K intake [10], and genetic factors [11,12]. In recent years, more emphasis has been put on establishing dosing algorithms that include these factors to achieve the optimal individual dosing strategy for coumarins. Several clinical trials were conducted to evaluate the effectiveness of these algorithms. The Clarification of Optimal Anticoagulation through Genetics (COAG) trial and the European Pharmacogenetics of Anticoagulants Therapy (EU-PACT) trial were randomized, multi-center, controlled trials conducted to assess the effect of genotype guided dosing for warfarin [13], acenocoumarol and phenprocoumon [14], respectively. These two trials had similar designs which compared the dosing algorithm including genetic information with an algorithm based on clinical parameters only that did not include genetic information. The result of the acenocoumarol and phenprocoumon arm of the EU-PACT trial indicated that there was no statistically significant difference between the genotype-guided algorithm and the clinical algorithm in the primary outcome of the trial (time in the therapeutic INR range during the 12 weeks of treatment) [14]. However, during the first 4 weeks of therapy, patients in the genotyped arm spend more time in therapeutic INR range. In contrast, the COAG trial showed no differences in percentage of time in therapeutic range in the initial 4 weeks of treatment between genotype-guided and clinically dosing algorithms. The warfarin arm of the EU-PACT trial assessed the clinical utility of genotype-guided warfarin dosing by comparing an algorithm containing clinical and genetic information with standard care (standard dose) [15]. This trial did show an effect on the primary endpoint: patients in the genotyped arm spent 7% more time in therapeutic range in the first 12 weeks of treatment [15]. However, because none of the trials included three treatment arms (standard care, clinical algorithm with and clinical algorithm without genetic information), it remains unclear what the effect of the use of the clinical dose algorithm without genetic information is versus standard care. Previously, the IWPC consortium showed that compared with a fixed dose approach, estimates from a clinical algorithm predicted warfarin actual stable dose better [16]. It is therefore hypothesized that the use of a clinical algorithm for acenocoumarol and phenprocoumon will result in a better outcome than standard care, and this might explain the different findings of the COAG trial [13], the EU-PACT acenocoumarol/phenprocoumon arm [14] and the EU-PACT warfarin arm [15]. The best way to make this comparison would of course be in a direct clinical trial. However, because it is highly unlikely that a clinical trial will be performed on this subject the aim of the present study is to compare the effect of a dose algorithm for acenocoumarol and phenprocoumon that included only clinical variables in the EU-PACT trial with a historic control group treated according to the standard care in the Netherlands.

Methods

Study Design and Study Population

For the present study, data of acenocoumarol and phenprocoumon patients who were treated in the Netherlands were obtained from the EU-PACT trial [14] and from the pre-EU-PACT study [17]. In brief, the EU-PACT was a multicenter, single blind, randomized, controlled trial designed to test the effectiveness of three genotype guided coumarins (acencoumarol, phenprocoumon, and warfarin) dosing respectively. The acenocoumarol trial was conducted in the Netherlands and in Greece, and the phenprocoumon trial was conducted in the Netherlands [14]. In the EU-PACT trial, patients of 18 years or older who were diagnosed with atrial fibrillation or venous thromboembolism and who had not received either acenocoumarol or phenprocoumon therapy preciously were enrolled and randomly assigned, in a 1:1 ratio to the use of a dosing algorithm that included both clinical information (age, sex, height, weight and amiodarone use) and genotype data for *VKORC1* and *CYP2C9* or to a dosing algorithm with only clinical information. For each group, patients received a dose according to a loading algorithm during the first 3 days and a dose-revision algorithm on days 4 or 5 determined by the clinical algorithm and first INR value. After day 5, dose was adjusted according to the INR results using local procedures. The patients were followed for 3 months with a target INR range of 2.0 to 3.0 [14]. In the present study, we only included patients dosed by the clinical algorithm and only used the data that were gathered in the Netherlands.

Data of the standard care group was from the observational pre-EU-PACT study, in which patients who were using acenocoumarol and phenprocoumon during November 2009 with a target INR in the lowest intensity category (according to Dutch guidelines INR 2.0-3.5) were included. Data was obtained from the electronic registry databases of the Anticoagulation Clinic Leiden (phenprocoumon) and the Anticoagulation Clinic Medial in Hoofddorp (acenocoumarol). These patients were treated according to standard care in the Netherlands, with the help of a computerized algorithm. In the pre-EU-PACT study, patients with an INR 1.5 or greater on the first day were excluded, because their treatment probably started earlier in a hospital or another thrombosis service, and therefore they were not incident starters with coumarin therapy. The Medical Ethics Committee of the Leiden University Medical Center approved both of the study protocols and patients provided informed consent before inclusion into the study. More detailed descriptions of the two studies can be found in earlier publications [14,17,18].

Outcome Measure

The primary outcome of the present study was the percentage of time in the therapeutic INR range (TTR) during 12 weeks after the initiation of acenocoumarol or phenprocoumon therapy. In the EU-PACT trial, all patients were treated with a target range of 2.0 to 3.0, while in pre-EU-PACT study the target was 2.0-3.5, according to standard practice in the Netherlands. Therefore, in this study, percentage of time in 2.0-3.5 was calculated. Percentage time in target range 2.0-3.0 was calculated as a sensitivity analysis. The percentage of time below (INR < 2), in (INR 2.0-3.5) and above (INR > 3.0 and INR > 3.5) the therapeutic range in both groups was compared. The TTR was calculated by using linear interpolation according to Rosendaal's method [19].

Statistical Analysis

Data for patients dosed according to the clinical algorithm in the present study was collected in different anticoagulation clinics. As a sensitivity analysis we performed center specific analyses using one-way ANOVA, there were no statistically significant differences in the clinical algorithm group for all outcomes in the different clinics (Supplement Fig. S3), therefore we pooled the data in the rest of the analyses. The mean differences of the TTR between the clinical dosing algorithm

from EU-PACT and standard care in the Netherlands from pre-EU-PACT with 95% confidence intervals (CIs) were calculated and compared with an independent-samples T test. The mean differences of TTR were adjusted for possible confounders using multiple linear regression. For acenocoumarol users, the adjustments were made for *CYP2C9* and *VKORC1* genotype, age, and indication. For phenprocoumon users, the adjustments were only made for *CYP2C9* and *VKORC1* genotype, and age. Indication was not used in the phenprocoumon model because it did not change the R Square in a univariate analysis.

Chi-Square Tests were used for comparison of categorical variables. Patients included in the analyses were treated at least 4 weeks. To increase power, patients with at least 10 weeks of follow-up were included for the analyses of 12 weeks except the separate analyses for the first 4 weeks and for weeks 5 through 8 which included patients with at least 4 weeks and 8 weeks follow-up, respectively. Two sensitivity analyses for the comparison of the primary outcomes were performed. In the first analysis only patients with at least 12 weeks follow-up were included. Because of the differences in study design the amount of INR measurements differed between the clinical algorithm and the standard care groups during the first month (see in the Supplement Table S1). We performed another sensitivity analysis that excluded measurements in the first week, and compared the TTR in week 2-12 weeks and 2-4 weeks between the groups. The number of measurements in the first week (as defined by the protocol) was much higher in the clinical trial, and this enlarges the chance of finding values outside therapeutic range. Therefore, we show the results of both 1-12 and 2-12 weeks. All analyses were performed with IBM SPSS Statistics version 20.0 (IBM Corp., USA).

Results

Patient Cohort

In this study we used data from the clinical algorithm group of the EU-PACT trial [14] and from the pre-EU-PACT study [17]. Of the 381 acenocoumarol users enrolled in the EU-PACT trial, 82 patients in the Netherlands were enrolled in the control arm and therefore eligible for the analyses in this study. Of the 471 acenocoumarol users in the pre-EU-PACT study, 272 patients were eligible for the present study. 1 pregnant patient, 113 patients who used phenprocoumon for a period of time during the first 3 months or who had a different target INR range, and 3 patients who changed anticoagulation clinics were excluded. Of the remaining patients, 65 patients who did not have a reliable start date, 14 patients who had an INR higher than 1.5 on the first day and 3 patients who had less than 2 INR measurements during the first 4 weeks were excluded. For phenprocoumon there were 167 patients in the EU-PACT trial. After excluding 83 patients treated according to genotype-guided dosing algorithm, 1 patient who withdrew the informed consent and 1 patient treated less than 4 weeks, 82 patients were included in the clinical algorithm group. Out of the 624 phenprocoumon users from the pre-EU-PACT study, 69 were excluded because they changed anticoagulation clinics, they were treated with acenocoumarol for a period of time during the first 3 months, or they had a different target INR range. Furthermore, 32 patients without a reliable start date, 37 patients with an INR greater than 1.5 on the first day, and 2 patients treated less than 4 weeks were excluded; therefore 484 patients were eligible in the present study. Patient characteristics are shown in Table 1. The selection flowchart can be found in the Supplement (Fig. S1 and S2).

There were no major differences between the clinical algorithm group and the standard care group in sex distribution or average height and weight (Table 1). The mean age in the clinical algorithm group for both acenocoumarol (65 versus 74) and phenprocoumon (67 versus 70) users was lower than that in the standard care group as shown in Table 1.

TTR for Acenocoumarol Users and Phenprocoumon Users

As shown in Table 2, among acenocoumarol users, the TTR in the clinical algorithm group was higher than the standard care group both during 12 weeks (mean difference 5.0%, 95%CI: 0.0 to 10.0) and the first 4 weeks (11.1%, 95%CI: 3.6 to 18.6). The sensitivity analyses that excluded the first week showed similar results. In adjusted analyses, the TTR differed by 6.2% (95% CI: 0.5 to 11.8) through week 2-12 and 12.2% (95%CI: 3.3 to 21.0) through week 2-4. The TTR of the clinical algorithm group in 9-12 weeks was also higher than that in standard

Table 1
Characteristics of included patients.

Characteristics	Acenocoumarol			Phenprocoumon		
	Clinical algorithm group (n = 82)	Standard care group (n = 272)	*P*-value	Clinical algorithm group (N = 82)	Standard care group (n = 484)	*P*-value
Male (%)	45 (54.9%)	153 (56.3%)	0.83	46(56.1%)	275 (56.8%)	0.90
Mean age, years	65 ± 13	74 ± 9	0.00	67 ± 11	70 ± 11	0.01
Mean height, cm	175 ± 11	173 ± 11	0.07	174 ± 10	173 ± 9	0.34
Mean weight, kg	86 ± 20	81 ± 19	0.06	83 ± 16	81 ± 17	0.42
Indications			0.01			0.16
Atrial fibrillation	62 (75.6%)	233 (85.7%)		68 (82.9%)	424 (87.6%)	
Venous thromboembolism	20 (24.4%)	32 (11.8%)		14 (17.1%)	52(10.7%)	
Others	-	7 (2.6%)		-	8 (1.7%)	
CYP2C9 genotype,			0.07			0.97
missing	-	10 (3.7%)		2 (2 %)	21 (4.3%)	
*1*1	50 (61%)	170 (63%)		56 (68%)	309 (64%)	
*1*2	14 (18%)	53 (20%)		14 (17%)	86 (18%)	
*1*3	11 (13%)	31 (11%)		7 (9%)	47 (10%)	
*2*2	6 (7%)	3 (1%)		2 (2%)	11 (2%)	
*2*3	1 (1%)	4 (2%)		1 (1%)	7 (1%)	
*3*3	0	1 (0)		0	3 (1%)	
HWE[†], *P*-value	0.02	0.94		0.77	0.33	
VKORC1 genotype			0.15			0.61
missing	-	9 (3.3%)		2 (2.4%)	20 (4.1%)	
GG	36 (44%)	91 (34%)		33 (40%)	174 (36)	
GA	33 (40%)	138 (51%)		33 (40%)	219 (45%)	
AA	13 (16%)	34 (13%)		14 (17%)	71 (15%)	
HWE, *P*-value	0.25	0.10		0.26	0.88	

[†] HWE denotes Hardy –Weinberg equilibrium.

Table 2
Percentage of time in the therapeutic range 2.0-3.5 during 12 weeks.*

	TTR (INR range 2.0-3.5)					
Analysis	Clinical algorithm group	n	Standard care group	n	Unadjusted Difference (95% CI)	Adjusted Difference # (95% CI)
Acenocoumarol						
Exclude the first week						
Week 2-12	74.3 ± 20.4	80	68.0 ± 20.6	271	6.3 (1.2 to 11.5) $	6.2 (0.5 to 11.8) $
Week 2-4	68.5 ± 33.5	82	53.2 ± 33.0	272	15.3 (7.1 to 23.5) $	12.2 (3.3 to 21.0) $
Week 5-8	71.3 ± 31.3	82	72.1 ± 29.5	272	-0.8 (-8.1 to 6.7)	0.8 (-7.3 to 9.0)
Week 9-12	80.6 ± 26.9	80	74.3 ± 30.4	271	6.3 (-0.7 to 13.3)	6.3 (-1.9 to 14.6)
Include the first week						
Week 1-12	71.8 ± 19.4	80	66.8 ± 20.1	271	5.0 (0.0 to 10.0) $	4.6 (-0.9 to 10.0)
Week 1-4	62.3 ± 28.6	82	51.2 ± 30.5	272	11.1 (3.6 to 18.6) $	7.6 (-0.4 to 15.5)
Phenprocoumon						
Exclude the first week						
Week 2-12	75.9 ± 21.5	80	70.1 ± 24.7	470	5.7 (-0.03 to 11.5)	4.5 (-1.3 to 10.3)
Week 2-4	60.9 ± 34.4	82	61.3 ± 34.5	484	-0.4 (-8.5 to 7.7)	-1.4 (-9.6 to 6.7)
Week 5-8	75.0 ± 29.2	82	69.6 ± 34.2	476	5.4 (-1.7 to 12.5)	4.3 (-3.6 to 12.2)
Week 9-12	87.6 ± 22.5	80	77.8 ± 31.1	470	9.8 (4.1 to 15.5) $	8.3 (1.2 to 15.5) $
Include the first week						
Week 1-12	71.3 ± 20.4	80	68.7 ± 23.4	470	2.8 (-2.8 to 8.1)	1.5 (-3.9 to 7.0)
Week 1-4	51.2 ± 27.3	82	58.2 ± 29.3	484	-7.1 (-13.9 to -0.3) $	-7.9 (-14.8 to -1.0) $

$ $P < 0.05$.
* Data were expressed as: mean ± SD.
# Adjusted for age, *CYP2C9* and *VKORC1* genotype (for acenocoumarol only), and indication.

care group (9.1 %, 95%CI: -0.2 to 18.4). During weeks 5 to 8, the TTR of the clinical algorithm group was a little lower than the standard care group.

For phenprocoumon users, during the 12 weeks initial treatment period, the clinical algorithm group obtained a 1.5% (95% CI: -3.9 to 7.0) improvement in the TTR compared with the standard care group (71.3% versus 68.7%). However, during the first 4 weeks, the clinical algorithm led to a clear -7.9% difference (95% CI: -14.8 to -1.0) compared with standard care. Without including the first week, the difference was 4.5% (95% CI: -1.3 to 10.3) and -1.4 % (95% CI: -9.6 to 6.7), respectively.

A sensitivity analyses was performed for the TTR in range 2.0-3.0, which gave similar results both for acenocoumarol and phenprocoumon, data are provided in the Supplement Table S2. The sensitivity analyses including data from patients with at least 12 weeks follow up also showed similar results (Supplement Tables S3 and S4).

Sub-therapeutic INR values

Fig. 1 shows the percentage of time with an INR < 2 in patients treated with acenocoumarol and phenprocoumon. Among acenocoumarol users in the clinical algorithm group the percentage of time with INR below 2 was less than in the standard care group during all the 12 weeks (clinical algorithm 19.5% vs. standard care 22.7%, 95%CI of the mean difference: -8.1 to 1.9) and the first 4 weeks (clinical algorithm 24.6% vs. standard care 38.9%, 95%CI of the mean difference: -21.4 to -7.1). In contrast with acenocoumarol users, the patients treated with phenprocoumon according to the clinical algorithm spent more time in INR range <2 than the standard care group, both in all the 12 weeks (clinical algorithm 19.3% versus standard care 13.1%, 95%CI of the mean difference: 1.7-10.0) and in the first 4 weeks (clinical algorithm 37.6% and standard care 22.8%; 95% CI of the mean difference: 7.8- 19.8). However, when we excluded the first week, the clinical algorithm and standard care differed only 2.9 % (95%CI: -1.5 to 7.2) in week 2 to 12, and 7.0 % (95% CI: 0.2 to 13.7) in week 2 to 4 (data are shown in the Supplement Tables S5 and S6).

Supra-therapeutic INR values

Fig. 2 shows the percentage of time with INR above 3.5. During the 12 weeks treatment period, acenocoumarol patients dosed according to the clinical care algorithm spent less time in INR above 3.5 than the standard care group (Fig. 2A). There is a declining trend of the percentage of time with INR above 3.5 in the clinical algorithm group, while in contrast, the time spent in INR above 3.5 increased with time in the standard care group. During the first 4 weeks the percentage of time above 3.5 in the clinical algorithm group was higher than with standard

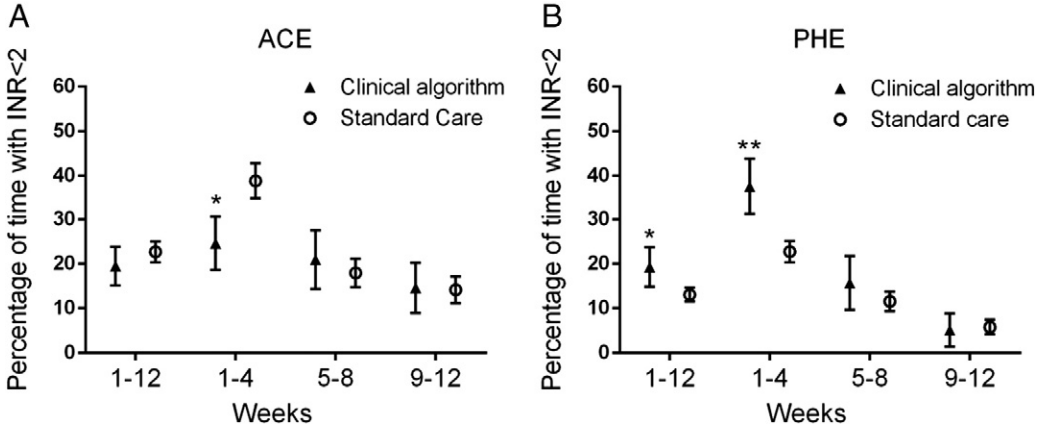

Fig. 1. Percentage of time with INR below 2 in different time periods; A: acenocoumarol (ACE); B: phenprocoumon (PHE). All the data are indicated as mean ± 95% confidence interval ($^{**}P < 0.01$; $^{*}P < 0.05$).

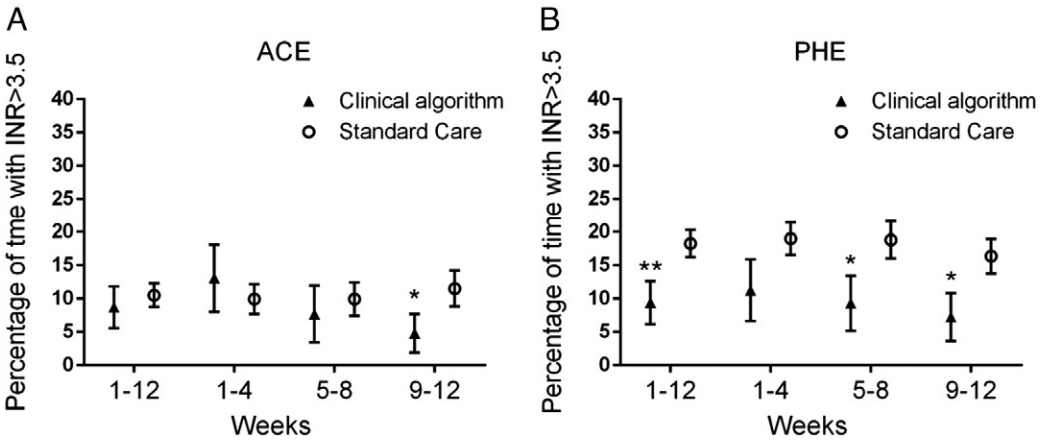

Fig. 2. Percentage of time with INR above 3.5 in different time periods; A: acenocoumarol (ACE); B: phenprocoumon (PHE). All the data are indicated as mean ± 95% confidence interval ($^{**}P < 0.01$; $^{*}P < 0.05$).

care. However, this situation was reversed in the last 4 weeks. In that period the percentage of time above 3.5 was statistically significantly lower (-6.3%, 95%CI of the mean difference: -12.0 to -0.5) in the clinical algorithm group. The sensitivity analysis that excluded the first week showed similar results and data are shown in the Supplement Table S5.

For phenprocoumon users, the percentage of time with INR above 3.5 is shown in Fig. 2B. Use of the clinical algorithm led to a lower percentage of time in INR range >3.5 both in all 12 weeks (clinical algorithm 9.4% vs. standard care 18.3%, 95%CI of the mean difference: -12.3to -2.4) and in first 4 weeks (-5.9%, 95%CI of the mean difference: -11.7 to 0.0). We also calculated the percentage of time with INR above 3 and results were similar as for INR above 3.5, therefore, data are provided in the Supplement Table S6.

Discussion

For the initiation of treatment with acenocoumarol or phenprocoumon the present study compared the use of a dosing algorithm that included clinical factors with standard care in the Netherlands. The clinical algorithm for both acenocoumarol and phenprocoumon led to a higher TTR during weeks 2-12 after the initiation of treatment, while only for acenocoumarol there was a significant difference.

Our data of the clinical algorithm were from the control group of the EU-PACT trial [14] which had a therapeutic INR range of 2.0-3.0, while according to clinical practice in the Netherlands, the therapeutic INR range was 2.0-3.5 for the therapy of atrial fibrillation or venous thromboembolism, therefore, we evaluated not only the TTR in both ranges but also the percentage of time below and above these ranges.

For acenocoumarol, there were no statistically significant differences between the clinical algorithm group and standard care group in the percentage of time with INR below 2 and above 3.5 during weeks 2-12. In contrast, in the clinical algorithm group, phenprocoumon users spent remarkably more time with INR below 2 but less time above 3.5 during the first 2-12 weeks. These findings indicate that using the clinical algorithm for acenocoumarol could lead to more benefit.

Because of the differences in study design the amount of INR measurements differed between the clinical algorithm and the standard care groups. According to the trial protocol all patients in the EU-PACT trial had a baseline INR measurement on the first day, with the second and the third measurement planned on day 4 and 6, respectively while in the pre-EU-PACT observational study the baseline INR measurement was not known and on average 1 INR measurement was conducted during the first 7 days. (Supplement Table S1). Consequently, in the standard care group, the calculated TTR and the percentage of time below and above the range during the first week could not be as accurate as that in the clinical algorithm group. This might have influenced our results. We therefore performed sensitivity analyses for all the outcomes by excluding the first week.

Our study used the percentage of time in, below and above the therapeutic range which is a reflection of anticoagulation quality, to evaluate the effectiveness of the clinical dosing algorithm [20,21]. However, earlier studies have showed that improvement in TTR led to an improvement in clinical outcomes [22,23]. The present study suggests that a clinical dosing algorithm could improve the TTR of acenocoumarol users. However, for phenprocoumon, the clinical algorithm may not be associated with more benefit because there were no statistically significant improvements in TTR during 2-12 weeks. Furthermore, although the clinical algorithm for phenprocoumon led to remarkable less time with INR above the range, it led to more time below the range as well, which may increase the risk of thromboembolism [20,24], especially during the initial 4 weeks of treatment.

It's interesting that we only detect a significant difference among acenocoumarol users between the clinical dosing algorithm group and the standard care. A possible explanation is that in the Netherlands, the long-acting phenprocoumon has been associated with a better quality of anticoagulation therapy than the short-acting acenocoumarol [25,26]. In our study, phenprocoumon users in the standard care group had a higher TTR compared with the acenoumourol users. While in the clinical algorithm group, the TTR of phenprocoumon users was similar to the TTR of the acenocoumarol users. For the acenocoumarol users there was more to gain with the clinical algorithm. This is a plausible explanation why there was a statistically significant difference for acenocoumarol users and not for the phenprocoumon users.

Another question to answer is whether the use of the clinical algorithm as a comparator may account for the difference in the results between the EU-PACT acenocoumarol/phenprocoumon arm and the EU-PACT warfarin arm. Combining the results from the trial and this study we drew a picture that compared three approaches for dosing acenocoumarol or phenprocoumon in the target INR range 2.0-3.0, (Fig. 3). The more information is considered, the more robust the dosing algorithm will be. Data from the acenocoumarol/phenprocoumon arm of the EU-PACT trial [14] indicate that during the first 12 weeks of treatment, genotype-guided dosing algorithm for acenocoumarol achieved approximately 3.4% more time in the therapeutic range (2.0-3.0) compared with the clinical algorithm, and for phenprocoumon, almost 2.5% more. However, both of the differences are not statistically significant. In our present study, this clinical dosing algorithm was compared with observational data using standard care in the Netherlands, which showed 3.5% improvement in TTR in range 2.0-3.0 for acenocoumarol and 6.5% for phenprocoumon during the first 12 weeks. Combining the genetic algorithm group of the acenocoumarol/phenprocoumon arm of the EU-PACT trial [14] and the present study, it seems that the

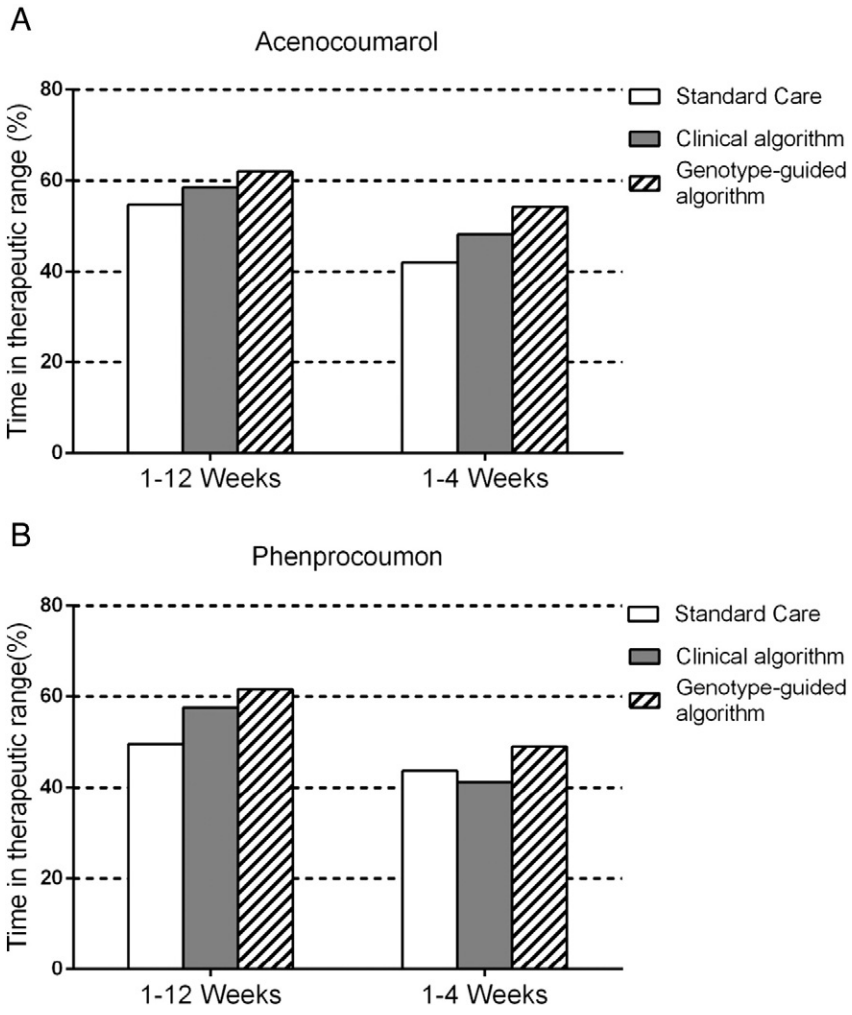

Fig. 3. Percentage of time in INR range 2.0-3.0 during 12 weeks and the first 4 weeks for standard care, clinical dosing and pharmacogenetic-guided dosing. A:acenocoumarol. B:phenprocoumon. Data of the genotype-guided group was from the Table 2 of the EU-PACT trial [1].

clinical dosing algorithm led to an improvement compared with the standard care and the genetic algorithm achieved even more improvement compared with the clinical algorithm group in TTR during 12 weeks of treatment while neither of these improvement was statistically significantly different. The difference in comparator between the EU-PACT acenocoumarol/phenprocoumon arm and the warfarin arm is partly account for the difference in the magnitude of the effect in both arms [15]. It is expected that compared with standard care, the use of an algorithm that includes both clinical factors and genotyping information will be the most optimal approach to predict acenocoumarol or phenprocoumon dose. However, it is unclear whether the small improvement is clinically relevant and cost-effective.

Our study has several limitations. First, the small number of patients in the clinical algorithm group caused a wide confidence interval, nevertheless we have detected a statistically significant difference. In addition, data used in the present study were derived from two studies that aimed at two different therapeutic INR ranges which will result in different way of dosing. When a higher target range is used, patient will naturally spend less time with a lower INR. Although we calculated the outcomes by using both INR ranges 2.0-3.0 and 2.0-3.5, interpretation problems remain. What's more, several variables may arise bias thus were used to correct the results. It is well known that with increasing age it is more difficult to keep the INR within the therapeutic range [27,28]. In our study, patients in the clinical algorithm group are on average younger than those in the standard care group, especially among acenocoumarol users. However, we do not expect that this has changed our results because we adjusted our results for age. Another variable is the genotype. However, there was no statistically significant difference in the distribution of *CYP2C9* and *VKORC1* genotypes between the clinical algorithm and the standard care groups. Therefore, the differences between groups in the present study were not caused by differences in frequencies of the *CYP2C9* and *VKORC1* genotypes but clinical factors. Finally, data of the clinical algorithm group was from a clinical trial while the standard care group was an observational study, which that might have influenced our results. However, also for the observational pre-EU-PACT study an informed consent had to be signed before inclusion. Therefore the patients in the observational study were a similar selection of the general population, and we do not expect that differences in source population will have influenced our results.

In conclusion, using a clinical dosing algorithm for acenocoumarol resulted in more time in therapeutic range compared with standard care during the first 12 weeks of treatment in the Netherlands. For phenprocoumon effects were in the same direction, but the difference was not statistically significant. The quality of anticoagulation therapy may be improved by using a clinical dosing algorithm without knowing the genotype. Moreover, since dosing by the clinical algorithm could improve the percentage of time in INR compared with the standard care, at least part of the difference between the outcome of the EU-PACT acenocoumarol/phenprocoumon arm and the EU-PACT warfarin arm can be explained by the use of the clinical dosing algorithm versus standard care.

Disclosure of Conflict of Interests

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Appendix A. Supplementary Data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.thromres.2015.04.034.

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