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ORIGINAL ARTICLE

Characteristics and quality of oral anticoagulation treatment in pediatric patients in the Netherlands based on the CAPS cohort

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Essentials

- The knowledge of quality and safety of acenocoumarol and phenprocoumon use in children is limited.
- We used data from a multicenter retrospective follow-up study in children in the Netherlands.
- The quality of anticoagulation control in the first month of use was low, but improved thereafter.
- No thromboembolic events occurred, however bleeding events occurred in 1–3 out of 10 patients.

Summary. *Background:* The use of vitamin-K antagonists in pediatric patients is rare and information on the quality and safety of treatment with acenocoumarol and phenprocoumon is limited. *Objectives:* To assess the quality, safety and effectiveness during the first year of acenocoumarol and phenprocoumon treatment in pediatric patients in the Netherlands. *Methods:* The Children Anticoagulation and Pharmacogenetics Study (CAPS) was designed as a multicenter retrospective follow-up study. Patients who used acenocoumarol or phenprocoumon at an age of $\leq$ 18 years, were selected from four pediatric hospitals and one anticoagulation clinic in the Netherlands. The quality of treatment was assessed by calculating the percentage of time in therapeutic INR range (TTR) for the first month and for every 3 months of use during the first year of treatment. Effectiveness and safety were assessed by the number of thromboembolic and bleeding events. *Results:* In total, 213 patients participated, of whom 187 (155 acenocoumarol; 32 phenprocoumon) were included in this analysis. The mean TTR was 47.0% and 51.4% in the first month of use for acenocoumarol and phenprocoumon, respectively. After the first 3 months the mean TTR for both VKAs was above 64%. In 14.6% (acenocoumarol) and 31.3% (phenprocoumon) of the patients a bleeding event occurred during the first year of treatment; no thromboembolic events were reported. *Conclusions:* The quality of anticoagulation treatment was low during the first month of use and leaves room for improvement. After the first month it increased to an acceptable level. However, bleeding events occurred frequently during the first year.

Keywords: acenocoumarol; adolescent; anticoagulants; child; infant; pediatrics; phenprocoumon.

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Introduction

Vitamin-K antagonists (VKAs) are used in children to treat or prevent thromboembolic events [1]. Other than those seen in adults, pediatric indications are dominated by congenital heart disease and its complications. Worldwide, warfarin is the most prescribed VKA. Therefore, most VKA-related research was focused on the use of

warfarin in adults. However, in several countries, including the Netherlands, Germany and Spain, acenocoumarol and/or phenprocoumon are used.

In relation to the pharmacokinetics and pharmacodynamics of drugs, it is commonly known that children cannot be considered as small-sized adults [2]. The metabolic and hemostatic systems are still in development, which influences the response to VKAs. Most knowledge on the kinetics and effectiveness of VKAs is obtained from adult patients. As a result, guidelines on the use of VKAs in children are based on relatively low-grade-quality evidence [1,3,4]. This makes it challenging to assess the required dose of VKAs in children, which can impair the quality, effectiveness and safety of the treatment.

The percentage of time in the therapeutic international normalized ratio (INR) range (TTR) is a frequently used parameter for the quality of VKA treatment. Anticoagulation is stated to be poor when the TTR is below 60–65%, because below this range VKAs and antiplatelet therapy have been shown to result in similar antithrombotic effectiveness in a population of adult patients with atrial fibrillation [5]. When the TTR is above 70% the anticoagulation control is defined as high by the European Society of Cardiology [6]. These definitions of anticoagulation control are all based on studies in adults. Considering there is no information available for pediatric patients, this is currently the only definition that can be used to classify the quality in pediatric patients.

The reported TTR in children using a VKA, mostly warfarin, varies between 39 and 92.9% [7–14]. The level of the TTR is largely dependent on differences in patient populations (i.e. age and genetic composition) and the management of VKA therapy (patient self-testing, patient self-management [self-testing and self-dosing], management by an anticoagulation clinic or general care strategies) [7,15]. Moreover, other factors play a role, such as the method of calculating the TTR, the type of VKA, if the TTR includes the initiation period of the VKA or not and the predefined therapeutic INR range (TR) [16–18].

This article presents the characteristics from the Children Anticoagulation and Pharmacogenetics Study (CAPS). Up to now acenocoumarol and phenprocoumon have not been widely studied in children. We assessed the quality, safety and effectiveness during the first year of acenocoumarol and phenprocoumon treatment in the Netherlands.

Methods

Study design

The study protocol from CAPS was approved by the UPPER Institutional Review Board of the Division of Pharmacoepidemiology and Clinical Pharmacology of Utrecht University. CAPS is a multicenter retrospective follow-up study in four pediatric hospitals in Amsterdam, Utrecht, Rotterdam and Groningen, and the Leiden anticoagulation clinic, in the Netherlands. CAPS was designed to study the pharmacogenetics of acenocoumarol and phenprocoumon in children. Children aged 18 years or younger, who used one of the two VKAs after 1 January 1995, were invited to participate. Patients (and/or their parents or legal guardians if appropriate for the age of the patient) who provided written informed consent were eligible for participation. The follow-up of a patient ended at the date of data collection at the anticoagulation clinic (between 11 January 2014 and 10 March 2016), when they became 19 years of age, when they stopped VKA therapy or when they were lost to follow-up. For these first analyses only the first year of use was taken into account. Patients were excluded from these analyses when the start date of VKA use was unknown or when no (valid) INR information was available within the first year. All data were collected using a digital form in the study database. No standardized method for information collection was available, because every hospital had a somewhat different system for storing the data (on paper/electronically). INR values, dosing information, indication, TR and weight and height were all retrospectively collected from the patient records of the hospital and the anticoagulation clinic(s) managing the VKA therapy of the patient. Furthermore, information was collected at the time that the informed consent was given by a short patient questionnaire, including questions about weight and height at the start of VKA use.

Quality assessment

For primary assessment of the quality of treatment, only patients using acenocoumarol or phenprocoumon for the first time during follow-up were included. To assess the quality of treatment, four parameters were calculated: the time to an INR in TR, TTR and the percentage of time below and above TR. Additionally, the number of INR measurements and the number of dose changes of more than 10% in mean daily dose between two INR measurements were calculated. The parameters were calculated for the first month and every 3 months during the first year of treatment. Patients had to fulfil the criteria specified in Table 1 to be included in the calculation of the specified parameter. The TTR was calculated using the Rosendaal method [19]. This method assumes linearity between two INR measurements. When there were 28 days or more between two INR measurements, linearity was no longer assumed and the time between these two INR measurements was not included in the TTR.

Effectiveness and safety assessment

Effectiveness and safety were assessed during the first year of treatment by the number of INRs below 2 (no therapeutic effect expected) or above 6 (increased risk of

Table 1 Criteria for calculating the quality parameters

		TTR + number of INR measurements			
	Time to INR in TR	First month	Months 1–3	Months 4–6/7–9/10–12	Number of dose changes of > 10%
INR within 5 days	x	x	x	–	–
No missing dose and INR information for ≥ 7 days during transition from hospital to anticoagulation clinic	x	x	x	–	–
Number of INRs/month required	–	≥ 3	≥ 2	≥ 1	–
No hospital readmission for surgery	–	x	x	–	–
≥ 90% of the daily dosages should be available for the specific period	–	–	–	–	x

INR, international normalized ratio; TR, therapeutic INR range; TTR, percentage of time in therapeutic INR range. *x*, required; –, not required.

bleeding events [20]), the use of vitamin K, and by reviewing the free text of the patient's records at the anticoagulation clinics for mention of both clinical or non-clinical bleeding or thrombotic events. Furthermore, the hospital records regarding correspondence on outpatient consultations, discharge letters and clinical notes during a hospital stay were checked for one of these events. Thromboembolic events were defined as new (recurrent/incident) thromboembolic events after the start of warfarin. Bleeding events were defined as all events describing an abnormal bleed somewhere in the body. All events were manually coded as types of event based on the location in the body.

Statistical analysis

To compare the characteristics of the acenocoumarol and phenprocoumon cohorts, a chi-squared test, an independent sample *t*-test or a Mann–Whitney *U*-test was used. Spearman correlation, independent sample *t*-test or one-way ANOVA were used to assess the associations between number of INR measurements, number of dose changes of more than 10%, age, TR, and patient self-testing with the TTR. Because of the low sample size these analyses were performed on all patients, without distinguishing between the two VKAs. Also, the difference in time below, within and above TR between patients with and without a bleeding event was tested using an independent sample *t*-test.

The data were analyzed using the statistical software SPSS version 23.

Results

In total, 573 pediatric patients who used a VKA, were identified and invited in writing to participate in the study. We were able to get in contact with 485 patients, and of these patients, 213 gave informed consent. Of these patients, 172 started with acenocoumarol, 34 with

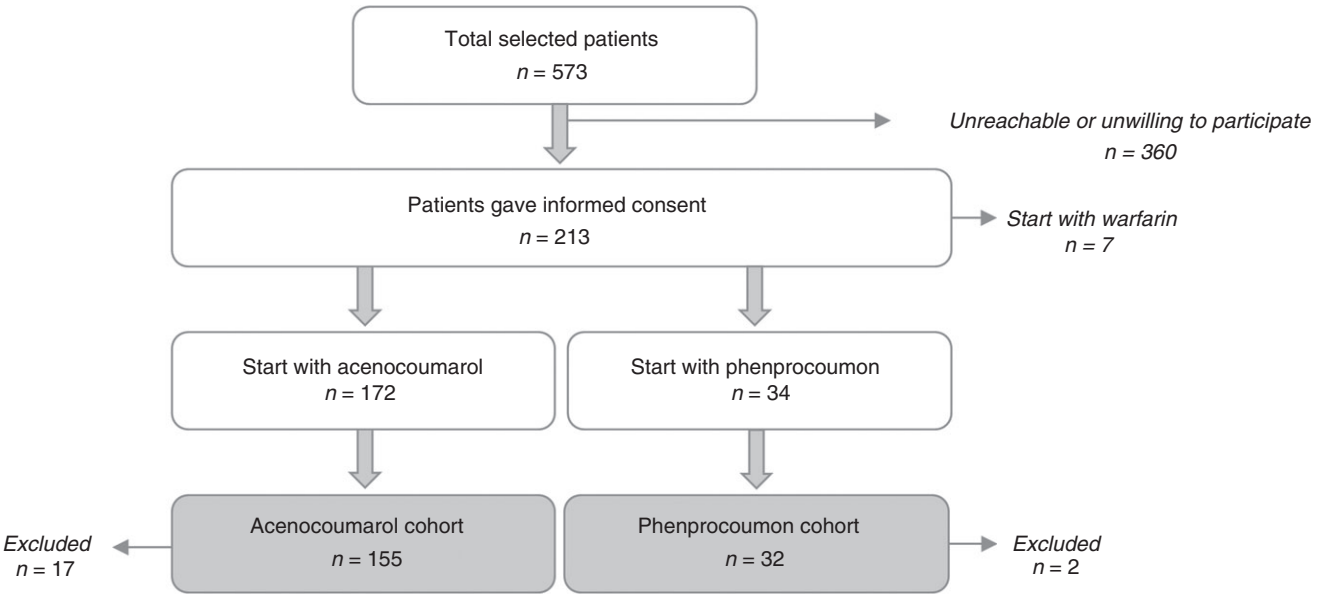

Fig. 1. Flowchart of the patients included in the acenocoumarol and phenprocoumon cohort.

phenprocoumon and seven with warfarin (see Fig. 1). Seventeen acenocoumarol and two phenprocoumon patients were excluded as a result of an unknown start date and/or no (valid) available INR measurements during the first year of VKA use. Furthermore, the seven patients who started on warfarin were excluded. Table 2 provides an overview of the characteristics of the acenocoumarol and phenprocoumon cohorts. The characteristics of the two cohorts differed statistically significantly in the distribution of age ($P = 0.001$), indication for VKA use ($P < 0.001$) and duration of VKA use ($P = 0.005$). An important difference between the two cohorts was the percentage of patients using the VKA for a cardiac indication. For acenocoumarol this was 63%; for phenprocoumon it was 38%. This difference in indication for VKA use also had an effect on the duration of use, which was more than 1 year for 58.1% of patients on acenocoumarol and 28.1% of patients on phenprocoumon (Table 2).

In the first year of the VKA treatment, patient self-testing occurred in 43.3% of patients for acenocoumarol and 34.4% for phenprocoumon. Only a small proportion of the patients using acenocoumarol (7.7%) had complete self-management (self-testing and self-dosing).

Quality of treatment

Within 7 days more than two-thirds of the patients had an INR within TR; within 14 days this percentage increased to more than 80%. The overall quality of

Table 2 Characteristics of the patients starting acenocoumarol or phenprocoumon therapy

	Acenocoumarol ($n = 155$)	Phenprocoumon ($n = 32$)	*P*-value
Gender (female), *n* (%)	75 (48.4)	17 (53.1)	0.625
Age at start of VKA use in years, *n* (%)			0.001
< 1	24 (15.5)	8 (25.0)	
1–3	37 (23.9)	7 (21.9)	
4–6	22 (14.2)	1 (3.1)	
7–9	17 (11.0)	0 (0)	
10–12	18 (11.6)	0 (0)	
13–15	22 (14.2)	5 (15.6)	
16–18	15 (9.7)	11 (34.4)	
European ethnicity, *n* (%)	131 (84.5)	29 (90.6)	0.580
Indication for anticoagulation, *n* (%)			<0.001
Fontan procedure	40 (25.8)	5 (15.6)	
Prosthetic heart valve	32 (20.6)	0 (0)	
Dilated cardiomyopathy	18 (11.6)	7 (21.9)	
Deep vein thrombosis/pulmonary embolism	48 (31.0)	13 (40.6)	
Aneurysm	4 (2.6)	0 (0)	
Pulmonary hypertension	2 (1.3)	0 (0)	
Cerebral*	4 (2.6)	2 (6.3)	
Prophylactic after surgical procedure†	0 (0)	5 (15.6)	
Other cardiac indication‡	6 (3.9)	0 (0)	
Antiphospholipid syndrome	1 (0.6)	0 (0)	
BMI at the start of VKA use§, median (IQR)	15.7 (14.2–17.6)	16.4 (15.1–21.1)	0.064
BSA at the start of VKA use§¶, median (IQR)	0.80 (0.57–1.31)	1.25 (0.61–1.83)	0.109
TR, *n* (%)			0.770
Extra low (2.0–2.5)	9 (5.8)	2 (6.3)	
Low (2.0–3.0)	27 (17.4)	4 (12.5)	
Standard (2.0–3.5)	82 (52.9)	21 (65.6)	
High (2.5–4.0)	33 (21.3)	5 (15.6)	
Extra high (3.5–4.5 [5])	4 (2.6)	0 (0.0)	
Duration of use, *n* (%)			0.005
< 3 months	20 (12.9)	10 (31.3)	
3–6 months	33 (21.3)	8 (25.0)	
6–12 months	10 (6.5)	3 (9.4)	
>1 year	90 (58.1)	9 (28.1)	
Unknown	2 (1.3)	2 (6.3)	
Patient self-testing, *n* (%)	67 (43.3)	11 (34.4)	0.433
Patient self-monitoring, *n* (%)	12 (7.7)	0 (0)	0.225
Switching between VKA, *n* (%)	17 (11.0)	2 (6.3)	0.167

VKA, vitamin K antagonist; BMI, body mass index; IQR, interquartile range; BSA, body surface area; TR, therapeutic international normalized ratio range. *Consists of sinus thrombosis ($n = 3$), cerebrovascular accident ($n = 2$), and cerebrovascular insufficiency with brainstem infarction ($n = 1$). †Consists of prophylactic use after a stent placement ($n = 2$) or orthopedic surgery ($n = 3$). ‡Consists of supraventricular tachycardia ($n = 3$), arrhythmia ($n = 1$), Blalock-Taussig shunt ($n = 1$) and impaired left ventricular function ($n = 1$). §Known for $n = 151$ (acenocoumarol) and $n = 29$ (phenprocoumon) patients. ¶Calculated using the formula of Haycock.

treatment, as expressed by the TTR, was 47.0% and 51.4% for users of acenocoumarol and phenprocoumon, respectively, during the first month of treatment (Fig. 2). When considering the first 3 months of treatment the TTR was 54.6% for acencocoumarol and 63.0% for phenprocoumon. After the first 3 months of treatment the TTR ranged between 64.7% and 69.1% for acenocoumarol and 65.8% and 75.4% for phenprocoumon in the 3-month periods thereafter. At the beginning of treatment, when out of TR, time was most often spent below TR. Later in treatment, this was shifting to a more equal division of the time out of TR between above and below TR (Fig. 2).

During the first month a large number of INR measurements was carried out (more than twice each week). In the months thereafter, this decreased to less than once a week. The frequency of dose changes of more than 10% decreased over time, from a median of 2.3 (acenocoumarol) and 3.2 (phenprocoumon) dose changes per month in the first 3 months to less than one dose change per month in the last 3 months of the first year (Table 3).

The TTR was negatively correlated ($P < 0.05$) with the number of INR measurements in the first 9 months of VKA treatment and with the number of dose changes during the first year (Table S1). For age, a positive correlation existed with the TTR in the first 3 months ($r = 0.398$, $P < 0.001$). In the rest of the first year of VKA treatment this effect was less clear, but there was still a trend towards a higher TTR with increasing age (Table S1). There was a trend for higher mean TTRs in patients who used patient self-testing compared with patients who were tested by an anticoagulation clinic.

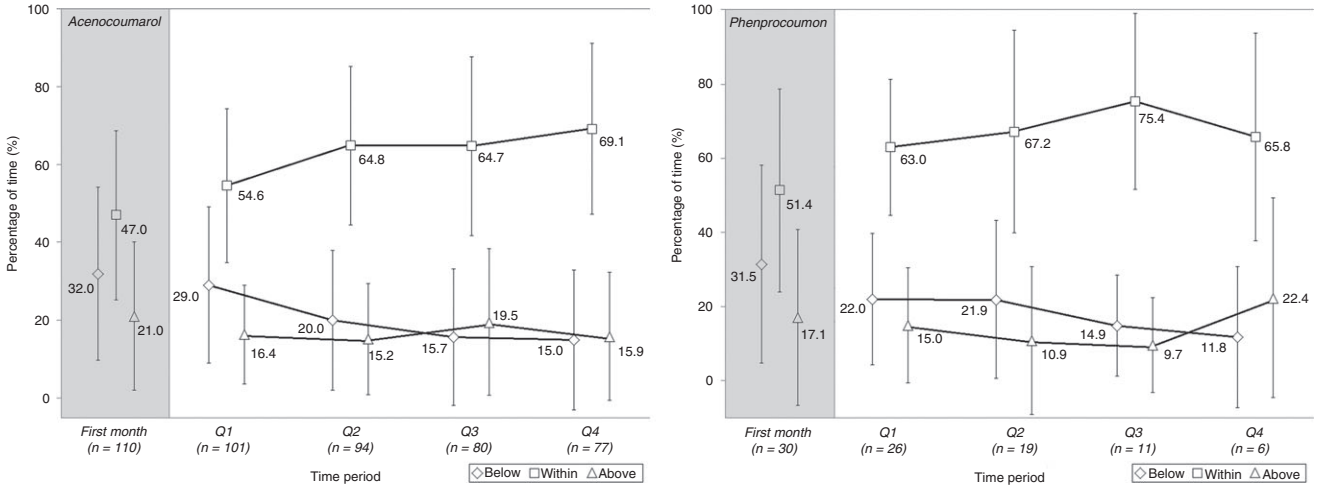

Fig. 2. The mean percentage of time below, within and above therapeutic INR range within the first month and months 1–3 (Q1), months 4–6 (Q2), months 7–9 (Q3) and months 10–12 (Q4) of the first year of acenocoumarol (left) and phenprocoumon (right) treatment. INR, international normalized ratio; Q, quarter.

Table 3 Treatment quality during the first year of treatment with acenocoumarol and phenprocoumon

	Acenocoumarol	n = 155	Phenprocoumon	n = 32
Achieving TR		139		31
≤ 7 days, n (%)*	106 (76.3)		21 (67.7)	
≤ 14 days, n (%)*	131 (94.2)		27 (87.1)	
Number of days, median (IQR)	4.0 (2.0-7.0)		4.0 (3.0-12.0)	
Number of INRs per month, median (IQR)				
< 1 month	10.0 (7.0–13.0)	110	9.0 (7.0–12.0)	30
Months 1–3	6.0 (4.7–7.7)	101	6.2 (4.3–10)	26
Months 4–6	3.7 (2.7–4.3)	94	4.3 (2.3–5.0)	19
Months 7–9	3.3 (2.5–4.3)	80	4.3 (2.0–4.3)	11
Months 10–12	3.0 (2.3–4.0)	77	2.7 (2.0–3.3)	6
Number of dose changes >10% per month, median (IQR)				
Months 1–3	2.3 (1.3–3.3)	152	3.2 (1.7–4.0)	32
Months 4–6	0.8 (0.3–2.0)	110	0.7 (0.3–3.0)	21
Months 7–9	0.7 (0.3–1.7)	91	1.0 (0.0–2.7)	14
Months 10–12	0.7 (0.0–1.3)	81	0.3 (0.0–1.0)	11

INR, international normalized ratio; TR, therapeutic INR range; IQR, interquartile range. *The percentages are based on the number of patients fulfilling the criteria for the parameter during that specific period, not on the total cohort.

Only for months 7 to 9 was the difference (12%) statistically significant (Table S2). There was a statistically significant difference ($P < 0.001$) between the TTR and the different TRs (Table S3). The patients with an extra low (2.0–2.5) or high (3.5–4.5/5) TR had a lower TTR compared with patients with a standard TR (2.0–3.5), which persisted throughout the year (Fig. 3).

Effectiveness and safety of treatment

During the first year of follow-up no (recurrent) thromboembolic events occurred. Bleeding events were quite common for both VKAs. They occurred at least once in 14.8% of the patients using acenocoumarol and in 31.3% of the patients using phenprocoumon (Table 4). The most commonly reported bleeding events were nosebleeds and (unexplained) bruising. None of the events could be explained by an INR value above 6 at the last measurement before the event. However, there seems to be a trend that patients with a bleeding event over the first year of treatment had a higher or equal percentage within, a lower or equal percentage below and a higher or equal percentage of time above therapeutic range compared with patients without a bleeding event (Table S4). Only in the third quarter of the first year was the percentage of time below therapeutic range statistically

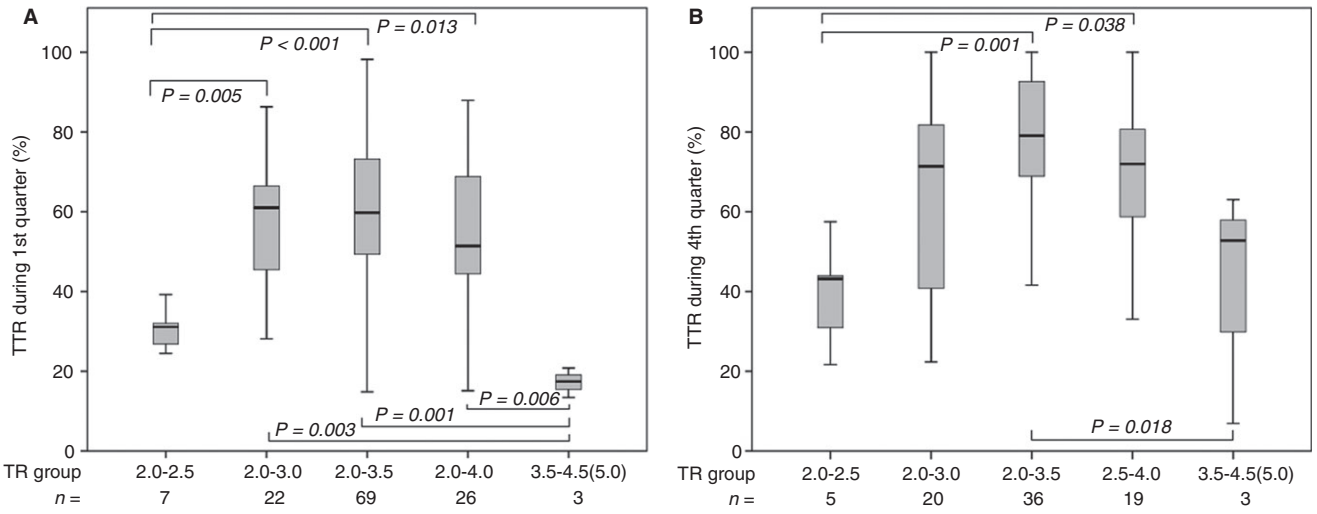

Fig. 3. Percentage of time in therapeutic INR range (TTR) by therapeutic range (TR) among users of acenocoumarol and phenprocoumon combined. (A) During the first 3 months of vitamin K antagonist (VKA) use. (B) During the last 3 months of the first year of VKA use.

Table 4 Effectiveness and safety parameters during the first year of acenocoumarol and phenprocoumon treatment.

	Acenocoumarol (n = 155)			Phenprocoumon (n = 32)		
	n (%)	Mean rate*	Mean fraction of total INRs‡, %	n (%)	Mean rate*	Mean fraction of total INRs‡, %
Thromboembolic events	0	0	–	0	0	–
Bleeding events	23 (14.8)	1.35	–	10 (31.3)	1.50	–
Type of bleeding event						
Nosebleed	13 (8.4)	4	–	2 (6.3)	2	–
Bruising with unknown cause	7 (4.5)	2	–	1 (3.1)	1	–
Increased bruising on impact	5 (3.2)	1	–	2 (6.3)	2	–
Hematuria	2 (1.3)	1	–	0	0	–
Blood in stool (melena)	1 (0.6)	1	–	1 (3.1)	1	–
Hematemesis	0	0	–	1 (3.1)	1	–
Eye bleeding	0	0	–	1 (3.1)	1	–
Other†	0	0	–	3 (9.4)	1	–
INR <2	153 (98.7)	8.96	33.2	30 (93.8)	8.93	28.3
INR >6	90 (58.1)	2.03	7.9	11 (34.4)	1.45	4.0
Use of vitamin K	13 (8.4)	1.15	–	11 (34.4)	1.18	–

INR, international normalized ratio; n, number of patients experiencing at least one event; –, not applicable. *For type of bleeding event the maximum rate is shown instead of the mean rate. †Consists of bleeding at an implantable cardioverter-defibrillator (n = 1) and prolonged bleeding after injury (n = 2). ‡Fraction of INR < 2 or > 6 of the total INR measurements of a patient.

significantly lower in the patients with a bleeding event compared with the patients without a bleeding event ($P = 0.001$).

Although there were no (recurrent) thromboembolic events during the first year, more than 90% of the patients experienced at least once an INR of less than 2 (Table 4). For both VKAs around one-third of the total number of INRs per patient was below 2. INRs higher than 6 occurred less frequently. These were present at least once in 58.1% and 34.4% of the acenocoumarol and phenprocoumon users, respectively. Furthermore, these INRs made up a small fraction of the total INRs per patient (7.9% for acenocoumarol and 4.0% for phenprocoumon). Not all INRs above 6 resulted in vitamin K administration. Only 8.4% of the patients were treated with vitamin K in the acenocoumarol cohort, which was statistically significantly ($P < 0.001$) lower than the 34.4% of the patients in the phenprocoumon cohort.

Discussion

The study shows that the quality (defined as the TTR) of VKA treatment in pediatric patients in the Netherlands is acceptable after the first 3 months of use. The TTR ranged between 64.7% and 69.1% for acenocoumarol and 65.8% and 75.4% for phenprocoumon. However, the TTR was lower during the first month (± 50%). Furthermore, the frequency of INR measurements and dose changes of more than 10% was high during the first 3 months of VKA treatment. Although the INR was frequently out of range and also in the extreme areas (< 2 and > 6), this was not associated with bleeding or thromboembolic events. However, a large proportion of the patients (14.8% for acenocoumarol and 31.3% for phenprocoumon) still had at least one bleeding event during the first year. No thromboembolic events were reported.

In adults, high (above 4–5) or low (below 2) INRs are correlated with major bleedings and thromboembolic events, respectively [20]. We were not able to find such associations. However, we did see that patients with bleeding events tended to have more time above range and less time below range, mostly not statistically significant, compared with patients without a bleeding event. However, because of the low number of events we didn't have enough power to study this. The number of complications could have been higher. Because of the retrospective nature of the study such complications may not have been retrieved. Another possibility is that events were prevented because of the intensive monitoring policy of the anticoagulation clinics with children on VKAs. In our cohort, INR measurements were carried out more often (three INR measurements/month) than recommended in the adult ACCP guideline of one INR measurement per 4–12 weeks [21], and the minimum of one INR measurement per month recommended for children [4]. This allows rapid dose adjustments when needed. Furthermore, the hemostatic system is still developing during childhood [22]. This might well be related to differences in risks of bleeding and thromboembolic events in comparison to adults.

Our TTRs were mostly higher (47–75.4%) than the TTRs found by Spoor *et al*. of just under 50% during the first year of treatment in children using acenocoumarol and phenprocoumon in the Netherlands [11]. A possible explanation for this difference is the larger proportion of patients in their cohort with a duration of follow-up/use of less than 3 months (46% compared with 16% in our cohort). In the first months, INR values show more fluctuation than in later periods, which reduces the overall TTR. This is also supported by our TTRs in the first month/first 3 months, which were around 50%. The TTRs of 65–75% after the first 3 months of treatment in our study are similar to the overall TTR of 63% found in the similar warfarin cohort of Biss *et al*. [8]. Our TTRs during the different time periods after the start of VKA therapy are also similar to the TTRs found in adults, changing from 54% in the first month to 75% after the first 3 months [23].

As expected, there was a clear association between the TR and the TTR during the first year. The TTR in the lower and narrower TR of 2.0–2.5 and the higher TR of 3.5–4.5 (5.0) were significantly lower compared with the TTR in children with a TR of 2.0–3.5. This is in line with the findings of previous studies in adults [17,18]. The study by Meier *et al*. showed that a narrow TR of 2.0–2.5 led to more INRs below 2 compared with a TR of 2.0–3.0 [18]. Gadisseur *et al*. showed that a TR of 2.5–3.5 resulted in a significantly higher TTR than a TR of 3.0–4.0 [17]. However, for both extreme TRs the numbers of patients were very low in our cohort. Furthermore, it is possible that patients were dosed with the aim of achieving a different TR than the one stated in the patient record, which reduces the calculated TTR. Interestingly, patients with the same indication often had different TRs stated in the patient records (data not shown). This indicates that possibly individual patient characteristics or the preference of the physician has an influence on the choice of the TR.

Although the TTR was on average indicative of an acceptable anticoagulation control, the standard deviation was large for both VKAs. For patients with low TTRs it is important to identify the causes (patient-specific and/or management-related factors) and to search for a way to improve these TTRs. Although we did not find any thromboembolic events in the first year, we did find that a large proportion of patients experienced bleeding events. Furthermore, the very frequent INR measurements and dose changes of more than 10% were common in the patients with lower TTRs, which can impair patient satisfaction and increase costs.

Earlier studies have shown that patients who self-test and self-manage can improve quality of life, patient

satisfaction and TTR [12,14,24]. As a result of the large standard deviations of the TTRs, we only found a statistically significant association between patient self-testing and the TTR during the seventh to ninth months of use. However, there was a clear trend of higher TTRs after the first 3 months for patients who were self-testing their INRs. Involving patients in their anticoagulation control by self-testing or self-management might be a way to improve the TTR, especially during the maintenance phase.

A meta-analysis of all randomized controlled trials in adults has shown that using a pharmacogenetic dosing algorithm increases the TTR, especially in the first months of use [25]. No such pediatric dosing algorithm exists yet for acenocoumarol and phenprocoumon. With the data from CAPS we will develop a pediatric pharmacogenetic-guided dosing algorithm for both VKAs. With this model it will be easier to predict the appropriate starting dose for individual patients, which might reduce the number of INR measurements and dose changes and increase the TTR.

A limitation of this study was the small number of patients, especially for phenprocoumon. Phenprocoumon is far less frequently used as a first VKA in pediatric patients in the Netherlands compared with acenocoumarol. Furthermore, the retrospective data collection might have resulted in incomplete or misinterpretation of data. With the available data we were not able to study the cause of low TTRs, such as diet, fever and/or concurrent drug therapy. Some information about concurrent drug therapy was available, but was too incomplete to use in the analysis. A strength of our study is that our cohort was composed of patients from different sites in the Netherlands, making it a representative sample of the Dutch pediatric population using VKAs. With the provided information on patient and treatment characteristics, physicians from other countries should be able to translate the results to their own situation.

In conclusion, the overall quality of acenocoumarol and phenprocoumon treatment in pediatric patients in the Netherlands is acceptable, but can be improved. Especially during the first month, the quality of VKA treatment is low, and during the first year of treatment a substantial number of bleeding events occurs. Developing a dosing algorithm can improve VKA anticoagulation and increase patient satisfaction, with fewer INR measurements, dose adjustments and possibly bleedings.

Addendum

H. Maagdenberg conducted the statistical analysis and wrote the manuscript. H. Maagdenberg, M. B. Bierings, A. H. Maitland-van der Zee and A. de Boer interpreted the results. A. H. Maitland-van der Zee, M. B. Bierings, A. de Boer, C. H. van Ommen, F. J. M. van der Meer, I. M. Appel and R. Y. J. Tamminga, all critically reviewed the manuscript. All authors contributed to the concept, design and the conduct of the study.

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Disclosure of Conflict of Interests

A. H. Maitland-van der Zee reports an unrestricted research grant from GSK, and a personal fee from AstraZeneca for taking part in an advisory board, outside the submitted work. The other authors state that they have no conflict of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. The association between TTR and number of INRs, number of dose changes of more than 10% and age during the first year of VKA use.
Table S2. The difference in mean TTR between patients who do and do not use self-testing during the first year of VKA use.
Table S3. The mean TTR of patients with different TRs during the first year of VKA use.
Table S4. Differences in percentage time below, within and above therapeutic INR range between patients with and without bleeding events.

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