

Comparison of the Quality of Oral Anticoagulant Therapy Through Patient Self-management and Management by Specialized Anticoagulation Clinics in the Netherlands

A Randomized Clinical Trial

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Background: Several studies have demonstrated that patient self-management of oral anticoagulant therapy (OAT) can improve treatment quality. However, most of these studies were not conducted within a specialized anticoagulation care system. The objective of the present study was to determine whether patient self-management of OAT improves the quality of care delivered by anticoagulation clinics.

Methods: In this randomized study by 2 Dutch anticoagulation clinics 341 patients aged between 18 and 75 years and receiving long-term OAT were divided into 4 groups: an existing routine care group of patients untrained in self-management; a routine care group of trained patients; a group managed weekly at an anticoagulation clinic where international normalized ratios were measured by trained patients; and weekly patient self-management. A 2-step randomization procedure was followed: first, a Zelen-design randomization was performed to distribute patients (without informing them) to the existing care group or to receive training in self-management; second, trained patients were randomized to the 3 other study groups.

Results: Only 25.6% of invited patients agreed to par-

ticipate in the training program. Patients who remained in the existing care group were within the international normalized ratio target range 63.5% of the time. The type of coumarin taken was a major predicting factor of OAT quality. In all study groups phenprocoumon outperformed acenocoumarol by 11.6% (95% confidence interval [CI], 6.6%-16.5%). Weekly management with phenprocoumon led to a 6.5% improvement (95% CI, 0.0%-13.1%) in time in the international normalized ratio target range when patients were managed at an anticoagulation clinic and to an 8.7% improvement (95% CI, 1.6%-15.9%) when patients were self-managed. Weekly management with acenocoumarol did not improve the quality of OAT.

Conclusion: With selected patients, the quality of OAT obtained through patient self-management is at least as high as that delivered by specialized physicians at anticoagulation clinics. Weekly management of OAT with long-acting phenprocoumon has to be preferred at anticoagulation clinics or, where possible, through patient self-management.

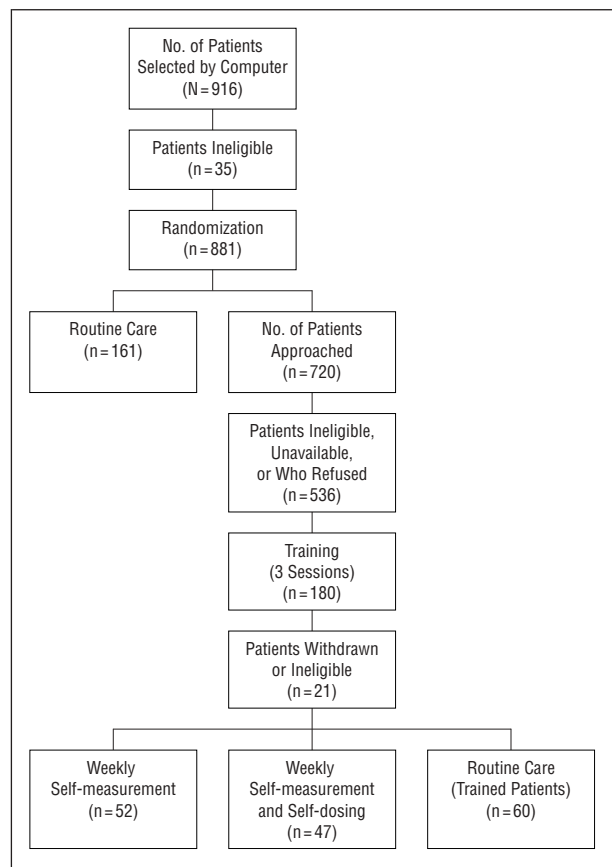
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ORAL ANTICOAGULANT therapy (OAT) with coumarin drugs is of vital importance in the treatment and prophylaxis of thromboembolic disease. The efficiency and relative safety of oral anticoagulants have been proven in clinical studies that have also led to define different therapeutic ranges for OAT for different indications. In many cases a minimal international normalized ratio (INR) of 2.0 to 2.5 is sufficient for efficient anticoagulation,¹⁻³ but indications with a high thromboembolic potential require more intensive anticoagulation. An increase in INR values is, however, associated with an increased risk of bleeding.⁴⁻⁷ This implies that

strictly maintaining the INR within the therapeutic range is required to ensure treatment efficacy with the lowest possible risks of thromboembolic and bleeding complications.

In reality, only 65% to 75% of the INR values measured during OAT have been found to be within the target range in the Netherlands,⁸ where a national network of anticoagulation clinics is responsible for the management of OAT.⁹ This has led to an improved management of OAT, resulting in a decrease in thromboembolic and bleeding complications. Frequent monitoring of prothrombin time (PT)/INR values continues to be an important part of the treatment, but it has physical, psychological, social, and financial conse-

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Study design showing patient numbers at each stage of the selection process.

quences for both patients and the health care system. Many patients believe that it interferes with their social or working life, and it is relatively costly and labor intensive for the health care system.

The development of handheld PT/INR measurement devices, which determine the PT from capillary whole blood, has led to the possibility of self-management of OAT. Several benefits of patient self-management have already been put forward by studies in which this new treatment modality was compared with the existing one.¹⁰⁻¹⁶ The potential advantages of self-management include improved convenience for the patients, which leads to better treatment compliance, more frequent monitoring, and, therefore, improved quality of OAT with fewer thromboembolic and hemorrhagic complications.¹⁷ Patient self-management of OAT is not necessarily less costly than existing care: a training system needs to be put in place,^{18,19} while handheld devices and test strips are expensive. There could be major cost benefits for the health care system, however, through a reduction in the number of complications.²⁰

Although these studies have indicated an improvement in the quality of OAT with self-management compared with conventional treatment, the existing system of treatment delivery mainly consisted of a diversity of treating physicians instead of a structured and specialized system of OAT management. Only 1 study so far has analyzed patient self-management in the Dutch system.²¹ In that study comparing weekly patient self-management with weekly management at an anticoagulation clinic, the patients outperformed the anticoagulation clinics by 6% in

time within the INR target range ($P = .07$). This study was performed with a highly selected patient group and did not allow for comparisons with the existing care system.

Performing an objective study comparing patient self-management of OAT with existing care is difficult. Many investigators either educate and train patients who are subsequently randomized for existing care or self-management, or limit training to the patients randomized for self-management. In these designs, comparisons between existing care and patient self-management are obscured by selection and confounding. When patients are trained for self-management but then return to the existing care system, this can no longer be defined as standard care owing to patient selection and education. When education and training are limited to the patients selected for self-management, it is unclear whether subsequently observed effects are caused by patient self-management itself or by increased patient awareness.

We compared the feasibility, safety, and efficacy of OAT self-management using the CoaguChek home PT monitoring device (Roche Diagnostics, Mannheim, Germany)²²⁻²⁴ with the quality of OAT management provided by the specialized system of Dutch anticoagulation clinics, in a way that evaluates the effect of patient training and self-management against the background of existing care.

METHODS

STUDY DESIGN

This study was performed by 2 Dutch anticoagulation clinics which, together, are responsible for the OAT of approximately 18000 patients per year. All relevant administrative data, clinical and laboratory parameters, and dosing schedules are kept in computerized files arranged according to randomly assigned 7-digit patient numbers. From this database we selected eligible patients on the basis of the following criteria: need for long-term OAT, at least 3 months of OAT experience, and age between 18 and 75 years. The investigators checked the patients' records for eligibility. Exclusion criteria were a diagnosis of antiphospholipid syndrome, a life-threatening illness, life expectancy less than 1 year, diminished understanding, and physical limitations making successful participation impossible (eg, dementia or tremors).

The patients were selected from the computer-generated list of patient numbers by groups of 40 and randomized to 4 treatment groups (A, B, C, and D) following a 2-step partial Zelen design. The patients randomized to group D were not informed of the study and therefore served as an "existing routine care" control group for whom treatment was not affected by the study. Patients who were not randomized to group D were contacted by letter by the investigators and received written information about the study. A return form was included in which they could indicate their willingness to participate in the study or give their reasons for declining to do so. If the form was not returned within 4 weeks, the patients were contacted by telephone and their reasons for not participating were recorded. Those who were willing to participate were invited to 3 training sessions. Cohorts were formed until a total of about 300 patients were actively included in the study, for a goal of 150 patients in group D (nontrained routine care), and 50 trained patients in groups A, B, and C. After successful training, randomization to groups A, B, or C was revealed to trainers and patients. All patients included in the study groups were followed up for 26 weeks. Study design and numbers of patients at each stage of the study are shown in the **Figure**.

Study protocol and patient information received approval from the medical ethics committee of the Leiden University Medical Center prior to the start of the study.

PATIENT GROUPS

In group A patients agreed to a weekly INR self-measurement but dosing was performed by anticoagulation clinic physicians. The patients reported their INR values by telephone to the anticoagulation clinics as well as any other relevant information about intercurrent medications, complications, or illnesses. The dosing schedules proposed by the physicians were sent by fax to the other participating anticoagulation clinic for correction in case of major mistakes. The patients were then contacted by telephone about their dosages for the coming week.

In group B, the group for weekly self-management of OAT, patients informed the anticoagulation clinic of their INR measurements, proposed dosing schedules, and reported any relevant information about intercurrent medications, complications, or illnesses. The proposed dosing schedules were sent by fax to the other anticoagulation clinic for correction in case of major mistakes. The patients were then contacted by telephone and told whether they could adhere to their proposed dosing schedule or if they needed to adjust it.

Patients in group C were trained for inclusion in groups A or B but stayed with the routine care system. Measurements of INR and dosing were done by anticoagulation clinic physicians, and the interval between measurements depended on the stability of the INR values.

Because patients in group D and dosing physicians were unaware of these patients' participation in the study, group D fully represented the general population in the existing care system. Measurements of INR and dosing were done by anticoagulation clinic physicians, and the intervals between measurements depended on the stability of the INR values.

BLINDING

Knowledge of the composition of the different groups was restricted to a few nurses who were also responsible for anonymously transferring the dosing schedules of group A and group B patients to standard forms and faxing them to the other participating anticoagulation clinic. The physicians evaluating and correcting the proposed dosing schedules for group A and group B patients were unaware of the originators of these schedules—patients in group B or physicians in group A.

The INR values of the patients in routine care groups C and D were entered into the routine computerized system in such a way that the dosing physicians could not distinguish between these and the general patient population.

PATIENT EDUCATION

All patients not randomized to group D underwent a training program consisting of 3 weekly sessions of 90 to 120 minutes. They received information about the study, the blood coagulation system, OAT, and the effects of some substances (eg, alcohol, certain medications, and foods rich in vitamin K) on OAT; then they were taught how to use the CoaguChek device, and instructed in oral self-dosing of phenprocoumon and acenocoumarol.

Training was done in groups of 4 to 5 patients by specialized teams consisting of a physician and paramedical personnel. A physician was always responsible for self-dosing instruction and was also present during training with the CoaguChek device. Teaching staff and patients were made aware of the groups (A, B, or C) to which patients were randomized only after the training had been completed.

Before the first training session the patients were given the opportunity to view, at home or at the anticoagulation clinic, a videotape about working with the CoaguChek PT monitor prepared by the manufacturer.

The first training session contained practical instruction about working with the CoaguChek PT monitor and information about the coagulation system, OAT, and the effects of some substances on OAT. The patients were given the opportunity to practice with the device at home during the week between the first and second training sessions.

During the second training session the patients had to be able to perform 2 accurate and reproducible INR measurements with the device unaided by the training staff, and the results were checked against a laboratory INR measurement from a venous blood sample. If there were wide differences (>20%) between laboratory and CoaguChek INR readings, patients were excluded. Theoretical and practical self-dosing training in OAT was given in the form of examples of dosing problems. The patients also received written information covering all subjects that had been discussed.

In the third training session self-dosing was discussed with the aid of practical dosing problems that the patients had prepared at home. Ability to work with the CoaguChek PT monitor was reassessed and randomization to the different patient groups (A, B, or C) was revealed to training staff and patients by the other participating anticoagulation clinic. The patients randomized for inclusion in group B (self-management) received a basic dosing schedule upon which they could base their own future dosage changes.

PT/INR MEASUREMENT

For laboratory PT/INR measurements, venous blood was collected in 105 mEq/L (105 mmol/L) of sodium citrate and plasma was obtained by centrifugation at 2800g for 10 minutes. To measure plasma PT, RecombiPlastin reagent (Ortho Diagnostic Systems, Rariton, NJ) was used with an Elektra 1800 coagulometer (Medical Laboratory Automation, Pleasantville, NY) at the Leiden anticoagulation clinic, and Innovin reagent (Dade Behring, Liederbach, Germany) was used with an Elektra 1400 coagulometer (Medical Laboratory Automation) at the Oost-Gelderland anticoagulation clinic. According to international convention, PT values were expressed as INR.

For patient PT/INR self-measurement, plasma PT was measured from a drop of capillary whole blood using the CoaguChek PT monitor. This device uses single-use test strips and rabbit brain thromboplastin as a reagent. A reagent master lot was calibrated by the manufacturer (Roche Diagnostics) against an international reference preparation for rabbit thromboplastin, and each production lot used in the study was calibrated against the master lot by the manufacturer. A code chip containing the information to convert PT into INR values accompanies each reagent lot. Lots 104, 129, 135, and 180 were used during the study.

RANDOMIZATION

Randomization was done in 2 steps by the participating anticoagulation clinic that the patients did not attend with a table of random numbers. The goal aimed at was to allot 50 patients to each of the groups A, B, and C, and 150 patients to group D. Only after completion of the training program was the investigating anticoagulation clinic told which patients were randomized to groups A, B, and C.

The first step was patient randomization to group D and to a non-D group (ie, collectively, the future groups A, B, and C). The proportion of patients randomized to group D was changed from 1:3 to 1:10 on the basis of response rates from

earlier groups. In a subsequent step, consenting patients from the non-D group were randomized to groups A, B, and C, which was revealed to the anticoagulation clinic that they did not attend only after training was completed. The ratio for randomization into groups A, B, or C was constant at 1:1:1.

DETERMINATION OF OAT DOSING SCHEDULES

Dosing of acenocoumarol and phenprocoumon is normally done by anticoagulation clinic physicians with the aid of a computerized dosing program (TRODIS; Infotrom, Leiden, the Netherlands). This program evaluates the stability of INR values and proposes dosing schedules for about 50% of the patients. These schedules are then checked by the physicians. For the other 50% of the patients, no dosage proposal is generated and dosing is done independently by the physicians. Details of the dosing algorithm have been published previously.²⁵

This routine dosing method was used for the patients in groups C and D. Patients in group A received their dosing from the same physicians but without the use of the computer algorithm. Dosing was determined on paper, in the way it was done by the patients themselves in group B.

Therapeutic INR target ranges are defined for all patients receiving OAT based on their indication for treatment. Two main therapeutic target ranges are used: low-level anticoagulation when INR values range from 2.5 to 3.5, and high-level anticoagulation when INR values range from 3.0 to 4.0.

Only 2 oral anticoagulants are registered in the Netherlands: short-acting acenocoumarol (half-life, 11 hours) and long-acting phenprocoumon (half-life, 140 hours).

END POINTS

The 2 following end points were defined a priori: (1) quality of OAT was represented by the number of INR readings within the target range, by the time spent within this range individually and per study group, and by the occurrence of thrombotic or hemorrhagic complications—data concerning complications were gathered from patients, general practitioners, and regional hospitals; and (2) patients' ability to independently perform anticoagulant self-dosing was considered inversely related to the number of dosage corrections made by the physicians.

STATISTICAL ANALYSIS

To determine OAT quality, INR readings "in range" and time values "in range" were used. These were, respectively, the percentage of all INR values within the therapeutic target range per patient and the estimated time spent within the therapeutic target range per patient based on the method of linear interpolation. This calculation method has been published previously.^{26,27}

With more than 1000 INR measurements expected in the 2 main study groups (A and B) and the group representing the existing system (D) the study was sufficiently powered to detect or exclude differences on the primary outcome. It was underpowered to detect any effects on clinical outcomes other than the largest, but the study was not primarily envisaged to look at the effects of the different coumarins.

The number of INR readings in range and the time in range are given as a percentage with 95% confidence intervals (CIs); the differences and the 95% CIs of the differences are based on the *t* distribution. Linear regression was used to identify predicting factors. The results of the linear regression analysis are given as β levels (standardized) and significance (*P* values).

Of the 916 patients randomly selected by computer, 35 (3.9%) were excluded because of intellectual or physical limitations or because of a life expectancy of less than 1 year.

Of the remaining 881 patients, 161 were randomized to control group D and 720 were contacted by a letter informing them about the study and asking for their participation in the training program. Only 184 (25.6%) of these 720 patients agreed to participate, and 536 (74.4%) refused. The reasons for not participating, personal answers to open questions, are given in the following tabulation:

Reason	Patients, No. (%)
Prefers existing system	178 (33.2)
Too old, nervous, or uncertain	132 (24.6)
Prefers not to contemplate illness	10 (1.9)
Personal reasons	14 (2.6)
Opposed to study design	6 (1.1)
No time or not interested	159 (29.7)
No response	37 (6.9)

Training was given to 180 of 184 patients (4 patients could not find the time). Of these, 21 (11.7%) were excluded during training for the following reasons: 9 patients did not succeed in working with the CoaguChek device, 8 patients had problems with self-dosing, 2 patients had differences greater than 20% between the laboratory INR measurement and their CoaguChek results, and 2 patients did not agree with the randomization process.

Group characteristics are given in **Table 1**. A total of 319 patients were studied with a mean follow-up time of 24.4 weeks, for a total of 149.5 patient-years. While the patients in groups A, B, and C were from the same computer-selected population as group D, self-selection brought about differences. The patients in groups A, B, and C were an average of 7.1 years younger than those in group D (95% CI, 4.7-9.5 years), and groups A, B, and C included more men than group D. However, linear regression analysis could not identify age as a predicting factor for time in range in a model containing age, sex, and type of coumarin ($\beta = -0.017$; $P = .83$). In contrast, the type of coumarin was a strong predictor for time in range ($\beta = 0.248$; $P < .001$) in this model. The ratios for the different INR target ranges, types of coumarin, and indications for OAT differed only slightly among the different groups. The indication for OAT was not identified as an important predicting factor.

The results of the different study groups for the number of INR readings within the therapeutic ranges (2.5-3.5 and 3.0-4.0) and the time spent in these ranges, overall and stratified by type of coumarin, are given in **Table 2**. Overall, time in range differed little between groups, and ranged between 63.5% and 68.6% of the time. The pattern became different when the type of coumarin was taken into account. Patients who used phenprocoumon in groups A and B had 72.9% and 75.1% of their INR readings in range, respectively, and clearly outperformed patients in control groups C and D who had 69.0% and 66.3% of their INR readings in range. The difference against the existing system (group D) for time in range with phenprocoumon was 8.7% (95% CI, 1.6%-15.9%) for group B (self-management) and 6.5% (95% CI,

Table 1. Group Characteristics

	Group A: Self-measurement of INR Values, Dosing by Anticoagulation Clinic	Group B: Self-measurement of INR Values, Self-dosing	Group C: Trained Patients, Routine Care	Group D: Untrained Patients, Routine Care
No. of patients	52	47	60	161
Sex, M/F	40/12	36/11	42/18	110/51
Mean age, y (range)	54.8 (25-74)	53.9 (24-75)	56.0 (21-73)	62.0 (32-75)
Target INR range, No. (%) of patients				
2.5-3.5	24 (46.2)	30 (65.2)	22 (36.7)	77 (47.8)
3.0-4.0	28 (53.8)	17 (34.8)	38 (63.3)	84 (52.2)
Anticoagulant, No. (%) of patients				
Phenprocoumon	34 (65.4)	31 (67.4)	51 (85.0)	108 (67.1)
Acenocoumarol	18 (34.6)	16 (32.6)	9 (15.0)	53 (32.9)
Indications, No. (%) of patients				
DVT/PE/venous TE	12 (23.1)	16 (34.0)	14 (23.0)	23 (14.3)
Arterial TE	1 (1.9)	1 (2.1)	2 (3.7)	3 (1.9)
Atrial fibrillation	6 (11.6)	9 (19.2)	10 (16.6)	43 (26.7)
Artificial heart valves	13 (25.0)	6 (12.8)	14 (23.2)	28 (17.4)
Cardiovascular prophylaxis	13 (25.0)	9 (19.1)	11 (18.5)	34 (21.1)
Cerebrovascular prophylaxis	1 (1.9)	1 (2.1)	0	3 (1.9)
Vascular prosthesis	4 (7.7)	3 (6.4)	8 (13.3)	21 (13.0)
Thrombophilia	2 (3.8)	2 (4.3)	1 (1.7)	6 (3.7)
Interval between INR readings, wk (range)	1.0	1.0	3.26 (1.0-6.25)	3.03 (1.0-5.2)
No. of INR values	1350	1180	565	1503
Total follow-up duration, wk	1298	1134	1458	3881
Mean follow-up duration, wk	25.0	24.7	24.3	24.1

Abbreviations: DVT, deep venous thrombosis; INR, international normalized ratio; PE, pulmonary embolism; TE, thromboembolism.

Table 2. Group Results for International Normalized Ratio (INR) Readings*

	Group A: Self-measurement of INR Values, Dosing by Anticoagulation Clinic	Group B: Self-measurement of INR Values, Self-dosing	Group C: Routine Care, Trained Patients	Group D: Routine Care, Untrained Patients	P Value†
No. of INR readings	1350	1180	565	1503	
Time, wk	1296	1134	1458	3881	
General analysis					
INR values in range	63.9 (59.8 to 68.0)	66.3 (61.0 to 71.5)	61.3 (55.4 to 67.1)	58.7 (55.0 to 62.4)	.14
Time in range	66.9 (62.7 to 71.0)	68.6 (63.7 to 73.6)	67.9 (62.9 to 73.0)	63.5 (59.7 to 67.3)	.33
Phenprocoumon					
INR values in range	69.3 (64.7 to 73.9)	74.0 (68.7 to 79.4)	63.0 (56.9 to 69.1)	62.1 (57.6 to 66.6)	.02
Time in range	72.9 (68.3 to 77.5)	75.1 (69.6 to 80.6)	69.0 (63.4 to 74.6)	66.3 (61.6 to 71.0)	.15
Acenocoumarol					
INR values in range	53.7 (48.0 to 59.4)	51.7 (44.3 to 59.2)	51.3 (30.8 to 71.7)	51.8 (45.4 to 58.2)	.99
Time in range	55.6 (50.3 to 60.9)	56.5 (49.4 to 63.6)	62.1 (48.2 to 76.1)	57.8 (51.7 to 63.9)	.86

*Values are given as percentage (95% confidence interval) unless otherwise indicated.

†P values are determined using analysis of variance for comparison between the 4 groups.

0.01%-13.0%) for group A (self-measurement, dosing by anticoagulation clinic) (**Table 3**). For patients taking acenocoumarol, there was almost no difference in INR readings in range between the groups, although group C did slightly better than the other groups, with 62.1%. Combining all groups, the percentages of INR readings in range ($\delta = 12.9\%$; 95% CI, 7.9%-17.9%) and of time in range ($\delta = 11.6\%$; 95% CI, 6.6%-16.5%) were higher with phenprocoumon than with acenocoumarol.

If we extend the INR target range to 2.0 to 4.0, the range that has been used in several studies dealing with patient self-management, a similar pattern is seen. Group D, which received the existing standard of care, was 86.3% of the time in range (88.8% of the time for patients tak-

ing phenprocoumon and 81.1% of the time for patients taking acenocoumarol). Group B, the self-managed group, was 91.0% of the time in range (94.3% of the time for patients taking phenprocoumon and 84.8% of the time for patients taking acenocoumarol).

When we compared, on a weekly basis, the self-dosing schedules of group A and group B patients with the schedules determined for them by the anticoagulation clinics' physicians, there was little difference (**Table 4**).

The effect of education about the blood coagulation system and OAT was assessed by comparing groups C (trained patients in general control) and D (general control). In both groups dosing was done by the antico-

Table 3. Group Differences in International Normalized Ratio (INR) Values With Existing System Represented by Group D (Routine Care)*

	Group A: Self-measurement of INR Values, Dosing by Anticoagulation Clinic	Group B: Self-measurement of INR Values, Self-dosing	Group C: Routine Care, Trained Patients
General analysis			
INR values in range	+5.2 (-1.7 to 12.1)	+7.6 (0.1 to 14.0)†	+2.6 (-4.4 to 9.6)
Time in range	+3.4 (-2.7 to 8.9)	+5.1 (-1.1 to 11.3)	+4.4 (-2.4 to 11.3)
Phenprocoumon			
INR values in range	+7.2 (0.8 to 13.6)†	+11.9 (3.0 to 20.7)†	+0.9 (-6.8 to 8.6)
Time in range	+6.5 (0.0 to 13.1)†	+8.7 (1.6 to 15.9)†	+2.6 (-5.2 to 10.4)
Acenocoumarol			
INR values in range	+1.9 (-6.5 to 10.2)	-0.1 (-12.4 to 12.3)	-0.5 (-17.7 to 16.6)
Time in range	-2.2 (-10.1 to 5.7)	-1.3 (-10.3 to 7.8)	+4.3 (-11.3 to 20.0)

*Values are given as percentage (95% confidence interval).

†Statistically significant at $P < .05$.

Table 4. Comparison of International Normalized Ratio (INR) Readings Between Group A and Group B*

	Group A: Self-measurement, Dosing by Anticoagulation Clinic	Group B: Self-measurement of INR Values, Self-dosing	Difference*
General analysis			
INR values in range	63.9 (59.8 to 68.0)	66.3 (61.0 to 71.5)	2.4 (-4.1 to 8.9)
Time in range	66.9 (62.7 to 71.0)	68.6 (63.7 to 73.6)	1.7 (-4.6 to 8.4)
Time <2.0	1.0 (0.4 to 1.7)	1.4 (0.2 to 2.6)	0.4 (-0.9 to 1.7)
Time >5.0	0.7 (0.2 to 1.1)	0.7 (0.2 to 1.2)	0.0 (-0.7 to 0.7)
Phenprocoumon			
INR values in range	69.3 (64.7 to 73.9)	74.0 (68.7 to 79.4)	4.7 (-2.2 to 11.6)
Time in range	72.9 (68.3 to 77.5)	75.1 (69.6 to 80.6)	2.2 (-4.8 to 9.2)
Time <2.0	0.7 (0.0 to 1.4)	0.3 (0.0 to 0.8)	-0.3 (-1.2 to 0.5)
Time >5.0	0.5 (0.0 to 1.1)	0.4 (0.0 to 0.8)	-0.2 (-0.9 to 0.5)
Acenocoumarol			
INR values in range	53.7 (48.0 to 59.4)	51.7 (44.3 to 59.2)	1.9 (-10.8 to 6.9)
Time in range	55.6 (50.3 to 60.9)	56.5 (49.4 to 63.6)	0.9 (-7.4 to 9.4)
Time <2.0	1.7 (0.2 to 3.2)	3.4 (0.1 to 6.7)	1.7 (-1.7 to 5.0)
Time >5.0	1.0 (0.2 to 1.8)	1.3 (0.0 to 2.7)	0.3 (-1.2 to 1.8)

*Values are given as percentage (95% confidence interval).

agulation clinics, with the intervals between INR measurements determined by the stability of the INR (Table 4). The trained patients seemed to have slightly better results ($\delta = 4.4\%$; 95% CI, -2.4% to 11.3%).

Table 5 shows weekly comparisons of INR measurements, the intervals between measurements being determined by INR stability and ranging from 1 to 6 weeks. Group A (weekly self-measurement) was compared with group C (group for which INR readings were done every 2.5 to 3.4 weeks). Overall, there was little difference in time in range between the 2 regimens ($\delta = -1.1\%$; 95% CI, -7.5% to 5.4%). When we stratified for the type of coumarin, however, different patterns emerged. There was an improvement in time in range ($\delta = 3.6\%$; 95% CI, -3.3% to 11.1%) for patients taking phenprocoumon when measurements and dosing were done on a weekly basis. In contrast, the weekly dosage change does not appear to be beneficial with acenocoumarol ($\delta = -6.5\%$; 95% CI, -20.1% to 7.9%).

Dosage corrections by blinded physicians could occur in groups A (self-measurement, dosing by anticoagulation clinic) and B (self-dosing). Generally, the number of corrections was low, at 3.7% of all dosage proposals.

There were more dose corrections in group B (5.2%) than in group A (2.4%). Most corrections concerned minor changes, and, in retrospect, did not seem necessary.

Major spontaneous hemorrhagic complications were few. In group B there was 1 case (0.045/patient-year) of a spontaneous subdural hematoma, in a patient with stable INR values in the target range during the previous 6 weeks and no INR values above 3.6 during the previous 18 weeks. There were 2 cases of gastrointestinal bleeding, 1 in the motivated control group C (0.036/patient-year) and 1 in the general control group D (0.013/patient-year). There were 2 cases of traumatic subdural hematoma, 1 each in group B and group C. There were no thromboembolic complications.

COMMENT

The recent development of patient self-management of OAT has the theoretical benefit of individually tailored therapy. Patients can adjust their dosing schedules with a more intimate knowledge of their own behavior and reactions to dose adjustments. Previous studies have suggested an increased quality of OAT through patient self-

Table 5. Comparison of International Normalized Ratio (INR) Readings Between Group A and Group C*

	Group A: Self-measurement, Dosing by Anticoagulation Clinic, Weekly INR Measurement	Group C: Routine Care, Trained Patients, INR Measurement Every 3.3 wk	Difference
General analysis			
INR values in range	63.9 (59.8 to 68.0)	61.3 (55.4 to 67.1)	2.6 (-4.6 to 9.7)
Time in range	66.9 (62.7 to 71.0)	67.9 (62.9 to 73.0)	-1.1 (-7.5 to 5.4)
Time INR <2.0	1.0 (0.4 to 1.7)	0.4 (0.0 to 0.9)	0.6 (-0.2 to 1.5)
Time INR >5.0	0.7 (0.2 to 1.1)	1.3 (0.2 to 2.3)	-0.6 (-1.7 to 0.6)
Phenprocoumon			
INR values in range	69.3 (64.7 to 73.9)	63.0 (56.9 to 69.1)	6.3 (-1.3 to 13.8)
Time in range	72.9 (68.3 to 77.5)	69.0 (63.4 to 74.6)	3.6 (-3.3 to 11.1)
Time <2.0	0.7 (0.0 to 1.4)	0.5 (0.0 to 1.0)	0.2 (-0.7 to 1.1)
Time >5.0	0.5 (0.0 to 1.1)	0.8 (0.0 to 1.7)	-0.3 (-1.3 to 0.7)
Acenocoumarol			
INR values in range	53.7 (48.0 to 59.4)	51.3 (30.8 to 71.7)	2.4 (-18.4 to 23.2)
Time in range	55.6 (50.3 to 60.9)	62.1 (48.2 to 76.1)	-6.5 (-21.0 to 7.9)
Time <2.0	1.7 (0.2 to 3.2)	0.0 (0.0 to 0.0)	1.7 (0.2 to 3.2)†
Time >5.0	1.0 (0.2 to 1.8)	4.0 (0.0 to 10.9)	-3.0 (-10.0 to 3.9)

*Values are given as percentage (95% confidence interval).

†Statistically significant at $P < .05$.

management compared with management by physicians. Our study is the first to compare patient self-management with management by a highly structured system of anticoagulation clinics in such a way that several aspects, such as the effect of patient selection and education, weekly management, and self-management are evaluated independently against the existing system.

In general, INR readings were only around 60% of the time within the target range with the existing routine system of OAT management. However, this range was relatively narrow. By extending the range to 2.0 to 4.0, as was done in most studies dealing with patient self-management, readings were within the therapeutic range more than 80% of the time, reflecting the high quality of routine OAT delivered by specialized anticoagulation clinics. In many of the studies conducted outside of specialized care facilities, INR readings were only 40% to 70% of the time within target range with an existing care delivery system.

Patients who consented to participate and received education had better readings than those in the current system. Several factors may explain this improvement. There may be a beneficial effect to increased patient education. However, most of the patients who were contacted for participation in the study declined to participate, and therefore the differences could also be attributed to selection.

It has recently become clear from various studies done in the Netherlands²⁸⁻³⁰ that long-acting phenprocoumon is associated with a better quality of anticoagulation than short-acting acenocoumarol. In the 4 study groups, the results with phenprocoumon use were superior to those with acenocoumarol use.

Can more frequent INR measurements, and consequently the possibility of more frequent dosage adjustments, improve the quality of OAT? In this study we looked at the effect of fixed weekly readings and dosing compared with that of INR readings and dosing about every 3 weeks depending on INR stability. There was a clear ad-

vantage to a weekly system for patients using phenprocoumon, contrasting with an important loss in time in range with weekly dosing of acenocoumarol. Weekly dosage corrections of short-acting acenocoumarol may create more numerous and stronger fluctuations in INR values than the wider-spaced corrections needed with long-acting phenprocoumon. It may be that fluctuations, which are inherent in a treatment with acenocoumarol, are further increased by frequent dose corrections. It is logical to prefer using the longer-acting and less fluctuating drug and avoid large dose adjustments.

In this study the largest improvements in time in range, compared with those obtained by the existing system, were reached with a combination of patient education and use of phenprocoumon, dosed weekly by anticoagulation clinic professionals and—with even better results—by patients themselves. From our results it is clear that selected patients are capable of delivering to themselves at least the same quality of OAT as the specialized anticoagulation clinics would deliver to them under the same conditions (ie, weekly INR measurements and dosing), and that they can even improve on it. Theoretically, one would expect the patients to be more able to tailor treatment to their individual circumstances. Our study had a follow-up of only 26 weeks, and it would be expected that the quality of self-management improves as patients become more experienced and learn more about their individual responses to dose changes.

Many of the patients in the self-management group opted to continue with this mode of treatment at the end of the study period, with visits to the anticoagulation clinic every 3 months. Taking into account the low percentage of participation in this study and the reasons for not participating, it is clear that self-management is a valid alternative treatment modality only for a relatively small proportion of anticoagulation clinic patients: younger, more active individuals possibly more attuned to information technology and receiving long-term anticoagulation. The quality of patient training and the availabil-

ity of medical and paramedical backup are of course crucial for the success of patient self-management. In this study patients underwent a rigorous training program and received intensive support from the investigators, which might not be available at most regular treatment facilities. It is clear that regular evaluation visits to the anticoagulation clinics are advisable.

In conclusion, this study has shown that patient self-management of OAT is an efficient and safe treatment modality in the Netherlands. Under the right conditions and for selected patients, self-management can provide an improvement in the quality of OAT currently delivered by anticoagulation clinics. Optimal-control OAT can be defined as a treatment with phenprocoumon rather than acenocoumarol. This treatment is based on frequent PT/INR measurements, which can easily be performed by the patients themselves with the aid of a home PT monitor and, where possible, managed by well-trained and well-supported patients who can adapt OAT to their particular circumstances and needs. For most patients, however, this treatment of choice must be received at specialized anticoagulation clinics.

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