

Oral anticoagulation self-management and management by a specialist anticoagulation clinic: a randomised cross-over comparison

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Summary

Background Vitamin K antagonist treatment is effective for prevention and treatment of thromboembolic events but frequent laboratory control and dose-adjustment are essential. Small portable devices have enabled patient self-monitoring of anticoagulation and self-adjustment of the dose. We compared this self-management of oral anticoagulant therapy with conventional management by a specialist anticoagulation clinic in a randomised cross-over study.

Methods 50 patients on long-term oral anticoagulant treatment were included in a randomised controlled crossover study. Patients were self-managed or were managed by the anticoagulation clinic for a period of 3 months. After this period the alternative strategy was followed for each patient. Prothrombin time (expressed as international normalised ratio [INR]) were measured at intervals of 1–2 weeks in both periods without knowledge of type of management. The primary endpoint was the number of measurements within the therapeutic range (therapeutic target value $\pm 50\cdot5$ INR units).

Findings There was no significant difference in the overall quality of control of anticoagulation between the two study periods. Patients were for 55% and for 49% of the treatment period within a range of $\pm 0\cdot5$ from the therapeutic target INR during self-management and anticoagulation clinic management, respectively ($p=0\cdot06$). The proportion of patients who spent most time in the therapeutic target range was larger during self-management than during anticoagulation clinic-guided management. The odds ratio for a better control of anticoagulation (defined as the period of time in the therapeutic target range) during self-management compared with anticoagulation clinic-guided management was 4·6 (95% CI 2·1–10·2). A patient-satisfaction assessment showed superiority of self-management over conventional care.

Interpretation Self-management of INR in the population in this study is feasible and appears to result in control of anticoagulation that is at least equivalent to management by a specialist anticoagulation clinic. It is also better appreciated by patients. Larger studies are required to assess the effect of this novel management strategy on the incidence of thromboembolic or bleeding complications.

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Introduction

Oral anticoagulant treatment with vitamin K antagonists, such as warfarin or coumarin derivatives, has been shown to be effective for the prevention and treatment of thromboembolic events in various clinical circumstances.^{1,2} Some patients need to be treated with vitamin K antagonists for a long time, even life-long, such as patients with mechanical prosthetic heart valves or patients with recurrent venous thromboembolism due to familial thrombophilia. The biological effect of these compounds—ie, inhibition of the synthesis of vitamin K-dependent coagulation factors—is extremely variable, both interindividually and intraindividually. Factors influencing this variability include fluctuating bioavailability, inconstant dietary vitamin K intake, changes in other drugs that the patient might be taking, and variable binding to plasma proteins.^{2,3} To prevent under-treatment or overdosing, regular laboratory control (by means of the prothrombin time, expressed as and referred to throughout this paper as international normalised ratio [INR]) of the intensity of anticoagulation and dose-adjustments are necessary.⁴ This management of oral anticoagulant therapy is often executed by hospital-based or specialised anticoagulation clinics, such as the “Thrombosis Service” in the Netherlands. Although this type of management is thought to be superior to less well-organised management of oral anticoagulation,^{5,6} and despite a strong organisation, laboratory quality control, and automated, computerised dose-adjustments, for many patients the intensity of anticoagulation does not fall within the “therapeutic target range” for long periods.^{7–10} Besides, the visits to the anticoagulation clinic are rather time-consuming and, for some patients, inconvenient.

Easy and reliable laboratory devices have become available, which allow the measurement of the prothrombin time (expressed as INR) from one drop of capillary whole blood.^{11–13} Application of these devices may allow patient self-testing of the intensity of anticoagulation and self-adjustment of the warfarin dose.¹⁴ Self-management of oral anticoagulant therapy may result in a more individualised approach, increased patient responsibility, and enhanced compliance, which may lead to improvement in the regulation of anticoagulation. An additional advantage could be that patients can do the test at home (saving travel and time during working hours) and are less dependent of the anticoagulation clinic. A potential disadvantage of self-management could be a poorer regulation of oral anticoagulant therapy, due to less professional guidance. Also, self-management of oral coagulation may theoretically be associated with increased anxiety of patients or even preoccupation with their disease.

Previous studies have shown the feasibility of self-testing and self-management of oral anticoagulation,^{15–19} while two investigations showed the potential superiority of self-management over that of general practitioners.^{20,21}

Self-management of anticoagulation has, however, so far not been compared with management by a specialised anticoagulation clinic. The aim of the present study was to directly compare the quality of self-management of oral anticoagulation with conventional care by the Thrombosis Service in the Netherlands in a randomised cross-over study.

Methods

Study design

The study was approved by the Institutional Review Board of the Academic Medical Centre of the University of Amsterdam, the Netherlands.

The study was done in two phases. In the first phase a direct comparison was made between self-measurement and self-dosing of vitamin K antagonists and anticoagulation-clinic-based management. The second phase of the study was done as a randomised cross-over study comparing self-management of oral anticoagulation with anticoagulation-clinic management.

In the first phase 15 patients on chronic (more than 6 months) anticoagulant therapy were educated and trained to measure their own INR and to adjust their dose of warfarin. Patients measured their INR at home at weekly intervals during a 6 week period. On the basis of this INR patients devised their own dosing schedule for the next week. Within 2 h they came to the anticoagulation clinic to have their INR measured using blood obtained by venipuncture. An experienced physician of the anticoagulation clinic then proposed a dosing scheme based on the anticoagulation-clinic INR value, in most cases with a computerised dosing program. This part of the study allowed us to establish the feasibility of self-measurement and self-dosing of anticoagulation by patients and the concordance between self-measured INR and clinic INR as well as between self-dosing of oral anticoagulation and physician-based dosing. The anticoagulation clinic INR and dosing scheme formed the basis for patient management.

In the randomised cross-over comparison (second phase) 50 patients on chronic anticoagulant therapy with oral agents were educated and trained to self-manage anticoagulation. Patients were then randomised (by sealed envelopes) to either 3 months of anticoagulation management by the specialised anticoagulation clinic (Thrombosis Service) or three months of self-management of anticoagulation. After 3 months, the alternative management strategy was used. To be able to assess the quality of anticoagulation in both study periods, the INR was measured at intervals of 1–2 weeks in all patients in both study periods by a central laboratory. These results were not made available to patients or managing physicians. The frequency of INR self-testing by patients during the self-management period and the frequency of INR determination by the Thrombosis Service during the anticoagulation clinic period was not more often than once weekly and at least once in 2 weeks. The primary endpoint of the study was the number of measurements that were within 0.5 INR units from the therapeutic target INR during each study period. Secondary endpoints included the percentage of time in the target range during the study period, the number of patients who were in the therapeutic target range for 0–100% of the time during each period, and the number of patients who achieved a better control of anticoagulation during one of the two management strategies.

Patients

Consecutive ambulant patients, seen at the outpatient departments of Cardiology and Internal Medicine of the Academic Medical Centre, Amsterdam, who received long-term anticoagulation and who were self-supporting were eligible for the study. The most important demographic and medical characteristics of the consenting patients are given in table 1. Indications for anticoagulation were prosthetic heart valves, prevention of arterial thrombosis (mostly in patients with atrial fibrillation), and secondary prevention of venous thromboembolism in patients with familial thrombophilia.

Education of patients

All patients underwent a structured educational programme to be able to do anticoagulation self-management. This educational programme was adapted from previously published educational programmes.^{21,22} Briefly, the program consisted of two 2 h sessions. In the first session a small group of patients (four to six per group) received structured and interactive teaching on the function of the coagulation system, and the principles and monitoring of anticoagulant therapy. Instructions on self-measurement of the INR by means of a capillary finger stick and use of an automated device was given via a video presentation and live demonstration. Patients were then given the opportunity to measure their own INR (at least once or as many times as they wished) in the presence of an instructor. In the 10 days between the first and the second session, patients had the opportunity to measure their INR in their own environment and to report their experience in the second session. This second session was also used to learn and practise how to devise a proper oral-anticoagulant dosing scheme. For teaching purposes, a standard dose-adaptation nomogram was used, but patients were encouraged to adjust and tailor this nomogram according to their individual experience. After concluding the educational programme patients started self-management of anticoagulation. A 24 h help desk was set up to answer any questions or to assist with any problem that might arise.

Measurement of INR

Venous blood (9 vol) was collected in 3.2% sodium citrate (1 vol) and plasma was obtained by centrifugation at 1800×g for 20 min. The prothrombin time (PT) was measured in plasma by Tromborel-S reagent (Dade Behring, Leusden, Netherlands, ISI value 1.19) on a Elekra 1600 coagulometer (MLA, Pleasantville, NY). PT values were expressed as an INR according to international convention. Self-measurement of INR was done on capillary blood (obtained by a fingertip puncture, Softclix lancet system) on a Coaguchek coagulometer (Roche Diagnostics, Almere, Netherlands), with Coaguchek PT teststrips (Roche Diagnostics).^{23,24}

Subjective quality of care assessment

A self-perceived assessment of the quality of care was made by patients using a structured questionnaire containing 32 items, which has been described previously.²¹ This questionnaire measures patients' feelings about oral anticoagulation, general treatment topics, treatment satisfaction, self-efficacy, daily frictions and worries, and social issues. For each category a minimum of 1 point (total dissatisfaction) and a

maximum of 6 points (complete satisfaction) could be scored. This assessment has been validated in a previous study.²¹ The questionnaire was submitted to the participating patients before and after they finished the period of self-management. A control group of patients on oral anticoagulation receiving regular anticoagulation-clinic-based care (matched for age, sex, and indication for anticoagulation) served as a reference population. The internal reliability coefficient of the questionnaire (Cronbach- α) was assessed as previously described.²⁵

Sample size and statistical analysis

All data are presented as mean (SD). The agreement between self-measurements and laboratory measurements in the initial phase of the study was analysed as previously described.^{26,27} The accuracy of the control of anticoagulation was assessed by evaluating the number of INR values within and outside the therapeutic target range and by measuring the length of time of adequate anticoagulation. The time in the therapeutic target range was calculated by means of linear interpolation.²⁸ The number of 50 patients for the randomised cross-over study was based on an assumption, as follows. From previous studies it can be concluded that, with Thrombosis-Service-managed anticoagulant therapy, at a given time about 20–40% of patients are not in the therapeutic target range.^{7–9} On the assumption that if 20% of patients are not in the therapeutic target range during the observation period (ie, 120 occasions per period), a significant difference of 15% or more (α -error 0.05, power 0.8) in accuracy of anticoagulation will be detected between the two groups with a total study population of 50 patients. If no such difference was observed, the management strategies could be considered to be equivalent. For comparisons of groups the Wilcoxon signed-rank test and two-tailed Fisher's exact test were used.

Results

Feasibility and safety of self-management

In the first phase of the study a direct comparison of INRs (self-measured and measured at the anticoagulation clinic) and warfarin-dosing schemes (self-devised or clinic-based) was made for the 6-week study period. All patients were able to measure the INR at home and to devise a dosing scheme for the next week. There was an acceptable correlation between the self-measured INR and the clinic INR (figure 1). The mean difference between all self-measurements and all clinic measurements was 12.3% (SD 10.1), with a κ value for the agreement between the two methods of 0.64 (limits of agreement 0.08 [1.04], weighed κ 0.46). The intra-class correlation coefficient was 0.91 (95% CI 0.86–0.95). A difference of more than 0.5 and 1.0 units of the self-measured INR from the corresponding clinic value was seen in 21% and 5% of the measurements, respectively. When analysed to find to what extent such a deviation of the test result would lead to a different dosing scheme (according to the proposed dosing algorithm), this would have been the case in 2% of measurements. The relation between the self-measured INR value (y) and the reference laboratory value could be expressed by the linear regression equation $y=0.993x-0.057$. The correlation (r) between the self-measured INR and the anticoagulation clinic INR was 0.85. As suggested by figure 1, patients

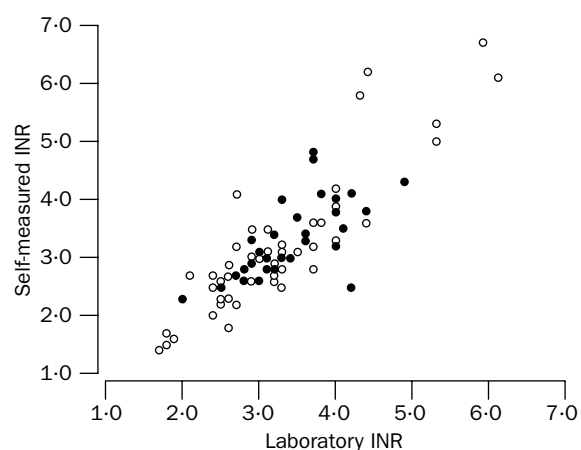


Figure 1: **Correlation between the self-measured INR from whole capillary blood at home and the virtually simultaneously measured laboratory INR from a venous blood sample**

The filled symbols and the open symbols represent measurements from patients taking phenprocoumon or acenocoumarol, respectively.

who were using phenprocoumon had a smaller variability in INR values than those who were using acenocoumarol, but this difference did not reach significance. There was also no relevant difference in the percentage of values within the therapeutic range between these two groups.

A good agreement was observed between self-devised and anticoagulation-clinic-prescribed dosing schemes. A complete agreement in dosing scheme (total week's dose of anticoagulant agent and division of this dose over the days of the week) was seen in 68% of the cases. The mean difference in self-proposed versus clinic-based dosing schemes (expressed as total week's dose of oral anticoagulant agent) was 4% (SD 10). A difference of 10% or more in dose between the self-devised scheme and the clinic scheme was found in 13% and a difference of 15% or more between the schemes was present in 2%. There was no discrepancy concerning the dosing schemes in divergent directions (ie, patients proposing to take a higher dose and clinic physicians proposing to take a lower dose) in any of the dosing schedules.

Comparison between self-management and thrombosis service

The frequency of INR determination in the self-management period was once every 8.6 days, compared with a test frequency of once every 9.0 days in the Thrombosis Service period.

Of the 50 patients included in this phase of the trial, one patient turned out to be unable to self-manage anticoagulation due to progressive visual impairment. All other patients were able to self-manage their anticoagulation during the study and the help-desk was infrequently consulted (0.3 times per patient in 3 months). In the remaining 49 patients the mean difference of all measured INRs from the therapeutic target value was 10% (SD 20) during the 3 months of self-management compared with 12% (22) in the period managed by the thrombosis service. There was no significant difference in the control of anticoagulation between the two study periods (figure 2). During self-management 55.0% of the measurements were less than 0.5 from the intended therapeutic target INR, whereas this figure was 49% in the Thrombosis Service management period ($p=0.06$, odds ratio 1.2, 95% CI

1.0–1.6). In particular, in patients in whom the control of anticoagulation was fairly good, the percentage of time in the target range was larger for patients on self-management than during management by the thrombosis service (figure 2). The number of patients having more than 50% of the time in the therapeutic target range (defined as the therapeutic target value ± 0.5) was 29 (60%) in the self-management period versus 25 (52%) in the thrombosis service period. The number of patients with more than 75% of the time in the therapeutic target range was 13 (27%) during self-management versus 6 (12%) in the thrombosis-service period (2.5, 1.0–6.7). Of the 49 patients 34 had a better control of anticoagulation (defined as the period of time in the therapeutic target range) during self-management than during anticoagulation clinic-guided management (4.6, 2.1–10.2). In five of 49 patients there was no difference and in ten of 49 patients the anticoagulation-clinic management resulted in a better control of anticoagulation than self-management. The number of dose adjustments was equal in both study periods and also the magnitude of the dose-adjustments was not significantly different between the two study periods. Serious under-anticoagulation or over-anticoagulation (INR <1.5 or >5.0) occurred during 3.5% of the self-management period and during 5.3% of the anticoagulation-clinic-management period ($p=0.07$).

No relation between a better control of anticoagulation and age, educational level, or indication for anticoagulation could be established.

No major bleeding episodes (defined as bleeding requiring hospital admission or transfusion or any central-nervous-system bleeding) were seen in either management group during the observation period. In the anticoagulation clinic-management group three minor bleedings occurred (one joint bleeding after minor trauma at an INR of 7.5, one minor calf-muscle bleeding at an

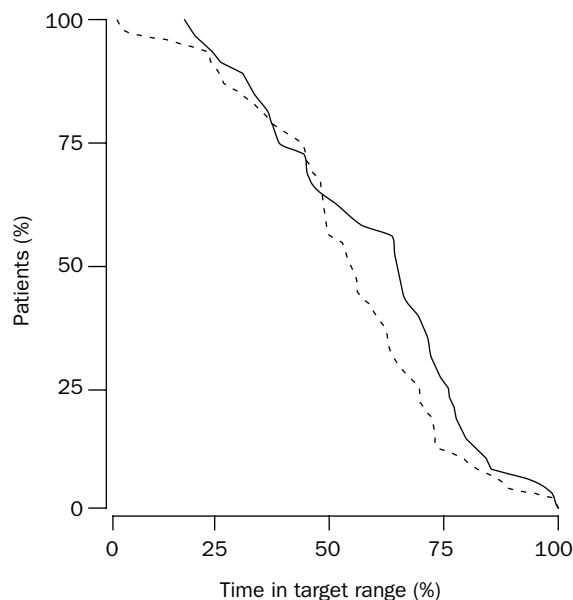


Figure 2: Comparison of control of anticoagulation (expressed as percentage of the time in the therapeutic target range) in patients during self-management (unbroken line) and during anticoagulation clinic-guided management (broken line)

Overall, there is no significant difference but the proportion of patients more than 50% of the time in the therapeutic target range is larger during self-management than during anticoagulation-clinic-based management ($p<0.05$).

| | Phase 1 (n=15) | Phase 2 (n=50) |
|---------------------------------------|------------------|------------------|
| Age (years) | 39 (range 19–58) | 42 (range 22–71) |
| M/F ratio | 7/8 | 29/20 |
| Indication for anticoagulation | | |
| Artificial heart valve | 5 (33%) | 23 (46%) |
| Arterial thromboembolism | 4 (27%) | 12 (24%) |
| Venous thromboembolism | 6 (40%) | 15 (30%) |
| Angiocoagulant agent | | |
| Acenocoumarol | 10 (67%) | 32 (64%) |
| Phenprocoumon | 5 (33%) | 18 (36%) |
| Aimed target range INR | | |
| 2.0–3.0 | 3 (20%) | 3 (6%) |
| 2.5–3.5 | 5 (33%) | 16 (32%) |
| 3.0–4.0 | 5 (33%) | 25 (50%) |
| 3.5–4.5 | 2 (14%) | 6 (12%) |

Table 1: Characteristics of patients in the INR comparison study (phase I) and in the cross-over comparison (phase II)

INR of 4.2, and one episode of recurrent nose bleeding at an INR of 6.5), whereas in the self-management period one minor nose bleeding (INR 2.4) occurred. In the anticoagulation-clinic-management period there was one episode of clinically suspected recurrent venous thrombosis (though not confirmed by objective testing) at an INR of 1.4 and one patient with a prosthetic aortic valve suffered from a transient ischaemic attack. During self-management there were no symptoms and signs of thrombotic complications. The differences in clinical outcome were not significant. The order of management in the study did not affect any of the outcome factors; in other words a carry-over effect could not be shown.

Subjective quality-of-care assessment

The quality-of-care questionnaire was completed by 45 participants at the start and the end of the self-management study period. A total of 44 patients on Thrombosis Service anticoagulation, matched for age, sex,

| | Self-management group (n=45) | Conventional-care group (n=44) | p | Cronbach- α |
|---|------------------------------|--------------------------------|--------|--------------------|
| Age | 42 (16) | 42 (12) | .. | .. |
| M/F ratio | 28:17 | 25:19 | .. | .. |
| Indication for anticoagulation | | | | |
| Artificial heart valve | 23 (51%) | 21 (48%) | | |
| Arterial thromboembolism | 12 (24%) | 10 (23%) | | |
| Venous thromboembolism | 10 (22%) | 12 (27%) | | |
| Target range INR | | | | |
| 2.0–3.0 | 2 (4%) | 2 (5%) | | |
| 2.5–3.5 | 13 (29%) | 16 (36%) | | |
| 3.0–4.0 | 24 (53%) | 22 (50%) | | |
| 3.5–4.5 | 6 (13%) | 4 (9%) | | |
| Years on anticoagulant treatment | 3.9 (2.2) | 4.1 (2.1) | | |
| Highest school education | | | | |
| University/advanced education | 20 (44%) | 19 (43%) | | |
| Intermediate education | 21 (47%) | 21 (48%) | | |
| Primary education | 4 (9%) | 4 (9%) | | |
| General treatment satisfaction | 4.8 (1.2) | 4.0 (1.5) | 0.015 | 0.74 |
| Self-efficacy | 5.4 (0.6) | 4.5 (1.0) | <0.001 | 0.70 |
| Daily worries | 1.8 (0.5) | 2.6 (0.5) | <0.001 | 0.83 |
| Distress | 2.5 (0.8) | 2.9 (1.1) | 0.022 | 0.76 |
| Social issues | 1.7 (0.6) | 2.7 (0.9) | <0.001 | 0.79 |

The comparison is made between patients participating in the cross-over study at the end of the self-management period and a matched control group receiving conventional care, ie, management of oral anticoagulation by the specialised anticoagulation clinic. Values are mean (SD).

Table 2: Patients' characteristics and comparison of subjective quality-of-care assessment

and indication for anticoagulation, formed the control group. Results from patients at the start of the self-management period were not different from the results obtained in the control group. There were no differences between the two groups in INR target ranges, number of years on anticoagulant treatment, and the degree of education (table 2). The internal reliability of the questionnaire was acceptable as indicated by the Cronbach- α values. There were significant differences in all five categories of the questionnaire in favour of the self-management group (table 2). Scores for general treatment satisfaction and self-efficacy were higher in the self-management group, whereas the score for daily anxieties, distress, and strain were significantly lower.

Discussion

Oral anticoagulation with warfarin is an effective measure for the treatment and prevention of arterial and venous thromboembolism. However, the substantial interindividual and intraindividual variation in the biological effect of vitamin K antagonists renders many patients outside the therapeutic target range over long periods of time. This is cumbersome for several reasons. First, clinical studies show that under-coagulation and over-coagulation enhance the risk of adverse clinical outcomes—ie, thromboembolism and bleeding, respectively.^{29–31} For example, the annual incidence of major bleeding in patients on vitamin K antagonists for various indications is 0.9–2.5% and this risk increases several-fold in patients with higher INRs. Hence, the variability in the intensity of anticoagulation necessitates frequent laboratory control and dose-adjustment, which constitutes a second drawback of oral anticoagulation. Previous studies have shown that anticoagulation management by specialised anticoagulation clinics results in better control of anticoagulation compared with control in general practice.^{5,6} However, in certain areas this may even amplify the practical problem of frequent checks. Self-management of anticoagulation may overcome the need for frequent visits to an anticoagulation clinic, may achieve maximal individualisation, and improved compliance, which are all factors that have been shown to improve the quality of anticoagulation.^{29–32} In our study we show that self-management of oral anticoagulation results in a control of anticoagulation that is at least as good and potentially superior to control by a specialised anticoagulation service in a randomised cross-over trial. Patients appeared to be able to measure their INR adequately and to devise appropriate dosing schemes for their warfarin. Some variation between the INR values obtained with the portable self-testing device and laboratory INRs was detectable. This is in accordance with previous reports, but in fact the variation was not larger than the variation that may be encountered between different laboratories measuring an INR value from a single sample.^{23,33} There was a slight benefit in the control of anticoagulation during the self-management period in comparison with the period that anticoagulation was managed by the anticoagulation clinic. In addition, patient-independence of the clinics considerably improved patient satisfaction with their anticoagulant treatment in comparison to patients receiving conventional care, which confirms identical findings in one of the previous studies.²¹ Previous studies have also shown the feasibility of self-management of

oral anticoagulation and a number of retrospective cohort studies have indicated that self-management of anticoagulant treatment was equivalent or superior to conventional care.^{156–18} Part of this effect may be explained by the feasibility of more frequent control of the INR. In multicentre prospective randomised trials it was shown that control of anticoagulation was better in patients who managed their anticoagulation themselves compared with patients who had their anticoagulation managed by a general practitioner.^{20,21} The present report is the first to indicate that self-management is at least as effective as management of anticoagulation by specialised anticoagulation centres.

In the present study the adequacy of anticoagulant control was expressed in terms of being in the therapeutic target range. In fact, the incidence of bleeding or thrombotic episodes would provide a potentially more relevant outcome assessment. However, the size and the design of our study did not permit us to establish a significant difference in these factors. Nevertheless, clinical studies show that there is a clear relation between adequate control of anticoagulation and a lower incidence of bleeding and thrombotic complications in patients on oral anticoagulants.^{9,29} Hence, the small improvement during self-management of oral anticoagulation, as shown in our study, may potentially be extrapolated to a beneficial effect of this management strategy on clinical outcome.

Although we did not specifically select patients for our study, a certain degree of selection cannot be excluded. Indeed, young patients or patients with a busy working or social life might be over-represented in our study group. Strictly speaking, we can limit our conclusions only to the feasibility of self-measurement of INR and self-dosing to the type of patients included in our study. However, others have found that all patients who are able to lead an independent and self-supporting life are in principle capable of self-management of anticoagulation, irrespective of education and social status. Other education and self-management programmes for patients, such as self-control and self-management of insulin-dependent diabetes mellitus, have been similar in this respect.³⁴ In our practice, limiting factors for self-measurement of the INR with the Coaguchek device were mainly physical factors, such as visual impairment. Another limitation of our study is that the results apply only to patients on chronic anticoagulant therapy and not to those just starting oral anticoagulant agents.

Despite the ability of patients to self-manage oral anticoagulation, adequate support remains necessary. Ongoing education, counsel in case of sustained dysregulation of anticoagulation, or advice on interruption of therapy in case of bleeding or the need to undergo an invasive procedure are, among others, issues that need to be taken care of. In the organisation of such support the anticoagulation clinics should play a major role. Nevertheless, self-management of anticoagulation may be a cost-effective approach, as was shown in a previous analysis.³⁵

In conclusion, we have shown that self-management of oral anticoagulant therapy is feasible and at least as effective as management by a specialised anticoagulation clinic. In addition, self-management was well accepted and appreciated by the participating patients. Self-

management of anticoagulation may be considered as a novel, patient-friendly, and effective strategy to improve long-term treatment with anticoagulant agents.

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