

A Structured Teaching and Self-management Program for Patients Receiving Oral Anticoagulation

A Randomized Controlled Trial

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ORAL ANTICOAGULANT therapy is increasingly used for prevention and treatment of various thromboembolic complications.¹ The aim of this therapy is to maintain levels of anticoagulation capable of preventing thromboembolic events without increasing the risk of hemorrhagic complications.² The risk of either complication depends largely on the time frame during which patients are outside the therapeutic range of prothrombin time (PT).^{2,3} Standard anticoagulation therapy requires frequent venous punctures and patients' visits to a physician's office or a laboratory and laboratory standardization. Interactions with other drugs⁴ and dietary influences⁵ can affect control. Furthermore, poor compliance with the prescribed treatment strategies and inadequate medical counseling have been identified as major factors for unstable control of anticoagulant therapy.⁶

In the treatment of diabetes mellitus and hypertension, self-monitoring and self-adjustment of medication dosage combined with structured patient teaching and treatment programs have resulted in major improvements of patient compliance, medical outcomes, and

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Context Control of oral anticoagulation therapy has been reported to often be inadequate. Previous retrospective investigations suggest that patients' self-adjustment of oral anticoagulants may lead to improved control.

Objective To investigate the effects of patients' self-management of oral anticoagulation therapy on accuracy of control and measures of treatment-related quality of life.

Design Randomized, single-blind, multicenter trial.

Setting and Participants A total of 179 patients receiving long-term oral anticoagulation treatment were enrolled at 5 referral centers in Germany.

Intervention Patients were randomized to an oral anticoagulation self-management group based on a structured treatment and teaching program and international normalized ratio (INR) self-monitoring. The control group received conventional care as provided by family physicians, including referral to specialists if necessary.

Main Outcome Measures Deviation of INR values from the individual INR target range (squared) and the 5 categories of treatment-related quality of life.

Results Deviation of INR value from the mean of the INR target range was significantly lower in the intervention group at 3-month (squared INR deviation, 0.59 vs 0.95; $P < .001$) and 6-month follow-up (0.65 vs 0.83; $P = .03$) compared with the control group. Also, the intervention group had INR values within the target range more often (repeated measurement analysis for categorical data, $P = .006$). The results were mainly due to less frequent suboptimal INR values in the intervention group (32.8% vs 50.0% [$P = .03$] at 3-month, and 33.7% vs 48.2% [$P = .08$] at 6-month follow-up). Treatment-related quality-of-life measures, especially treatment satisfaction scores, were significantly higher in the intervention group compared with controls.

Conclusions An anticoagulation education program that includes self-management of anticoagulation therapy results in improved accuracy of anticoagulation control and in treatment-related quality-of-life measures. Further studies are needed to describe whether the program will reduce risk of bleeding or thromboembolism.

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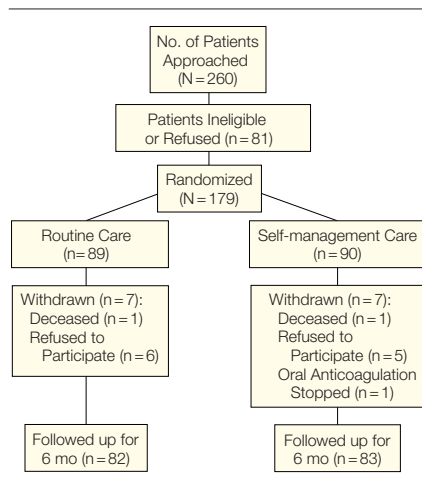
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quality of life.^{7,8} The use of portable capillary whole-blood analyzers combined with an effective self-management program for patients could likewise improve the outcome for anticoagulation. Ansell et al^{9,10} reported in retrospective and prospective uncontrolled studies that

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Figure. Enrollment and Scheduled Follow-up in the Structured Teaching and Self-Management Program for Patients Receiving Oral Anticoagulation



patient self-management of oral anticoagulation based on self-measurement of PT is feasible and safe and results in control at least as good as in a specialized anticoagulation clinic. The current multicenter, randomized trial was designed to determine the effect of a structured educational program aimed at self-management of anticoagulation therapy. The success of the therapy was based on the quality of care as defined by achievement of international normalized ratio (INR) values within the target range and treatment-related quality of life compared with conventional care.

METHODS

Patients and Inclusion Criteria

Five departments specializing in the treatment of patients receiving oral anticoagulation therapy participated in this multicenter study. The centers were advised to screen all consecutive patients with oral anticoagulant treatment appearing at the respective center. If the inclusion criteria were met and the patient agreed to participate in the study, the patient reported to the coordinating center (FIGURE). Patients who had not been previously treated in these centers, who had a disease or condition expected to require life-long anticoagu-

lant treatment, and who agreed to participate were enrolled. No other preselection was done. The study's statistician randomized all patients at the coordinating center by means of a computer program. A separate randomization table was used for each center to ensure an even distribution of patients to both study groups in each center.

The study protocol was approved by the ethical committees of all participating centers. All patients gave their written informed consent to participate in the study. The family physicians of all the patients were informed about the study. The oral anticoagulant was phenprocoumon. Before enrollment into the study, the INR therapeutic target range was defined individually by the treating physicians and reported to all patients. In patients with prosthetic heart valve replacement, the INR target range was, in most cases, 3.0 to 4.0, 3.0 to 4.5, or 2.5 to 3.5,¹¹ and in those with atrial fibrillation it was 2.0 to 3.0. However, in some patients, the treating physician defined a rather narrow INR range, for example 3.0 to 3.5. All INR target ranges were also documented in patients' log books at baseline; they remained unchanged throughout the trial.

Control Group

The control group, usual outpatient care, consisted of twice monthly visits to a family practitioner or an outpatient clinic. During these visits, blood was drawn by the physician or the laboratory to determine the INR value. When necessary, the family physician advised the control group patient with regard to the change in the anticoagulant dosage. The treating physicians provided the control group patients with unstructured information about oral anticoagulants, diet, and adverse effects. The control group patients were asked to refrain from self-monitoring and self-management of anticoagulation for 6 months until the end of the study, when participation in the self-management program would also be offered to them. Control patients with INR values out of range at baseline and at 3-month follow-up were advised to see their physician.

Intervention

A structured educational program was developed and all teaching nurses and physicians responsible for the education of the patients in the intervention group participated in a 2-day training course. The goal of the oral anticoagulation teaching and self-management program was to help patients assume increased responsibility for disease management based on systematic INR value self-monitoring and self-management of the anticoagulant dosage. The program consisted of 3 consecutive weekly teaching sessions of 60 to 90 minutes for groups of 3 to 6 patients. During the first session, patients were informed about anticoagulation in general and received extensive training in INR value self-monitoring using a whole blood PT/INR monitor (CoaguChek, Boehringer Mannheim, Mannheim, Germany).¹² During the first week, the patients were encouraged to measure INR values routinely and to record the results and the anticoagulant dosages in their log book. The topics of the second session included instructions to prevent bleeding and thromboembolic complications and the effect of diet and additional medication on anticoagulation control. During the second and the third session, patients were instructed about indications and models of reducing or increasing the anticoagulant dosages to achieve INR values within the target range. Several examples of adapting drug dosage were discussed and practice exercises were completed by the patients. In addition, possible problems that might be encountered with operations, illness, exercise, pregnancy, and traveling were discussed. The quality of INR value self-monitoring was checked by the teaching nurse at the end of the first and at the beginning of the following 2 sessions. After participation in the program, the patients had to estimate their INR value with an absolute deviation of less than 0.4 from the reference value. If this was not the case, then the training was repeated. At the end of the training all patients who participated in the study achieved INR measurements with deviations of less than 0.4 from the ref-

erence INR measurement. After participation in the program, the patients were encouraged to control the INR values by self-monitoring 1 to 2 times per week, to adjust their anticoagulant dosage accordingly, and to contact the teaching center in case of difficulties.

Outcome Measures

Patient examinations were scheduled at baseline and at 3 and 6 months after randomization. At baseline and at both follow-up visits, plasma was obtained from 9 mL of whole blood anticoagulated with 1 mL of sodium citrate, followed by centrifugation at 2000g for 30 minutes. For laboratory measurement of INR values, all samples were stored at -70°C until after the end of the study, when PT was measured using an automated coagulation laboratory instrument (Behring Coagulation System, Behring Diagnostics) with a single charge of a Thromborel-S (Behring Diagnostics). Laboratory measurement of PTs and the corresponding INR values was performed by a technician and a documentation assistant who were blinded to the treatment arm of the study. Anticoagulation was assessed at baseline and at 3- and 6-month follow-up. To simultaneously evaluate positive and negative differences between the INR target range and INR values, the squared INR value deviation was assessed with the following equation:

$$\text{Squared INR Value Deviation} = [\text{INR} - \frac{1}{2}(\text{Upper Value of Target INR Range} + \text{Lower Value of Target INR Range})]^2.$$

To detect a difference of 0.5 regarding the means of the squared INR value deviation between the groups with a power of 90%, a sample size of 86 patients per group was needed, assuming a significance level of $P = .05$ and SD of the squared INR value deviation of 1.0 in each group.

In addition to the assessment of the squared deviation of the INR values, the laboratory INR values were also rated in relation to the individual INR target range for each patient as to whether they were inside or outside of the target range. This evaluation was performed by an independent person (Mr Johannsen) who was

not directly involved in the study and was blinded to the treatment arm. At baseline and at 6-month follow-up, treatment-related quality of life was assessed using a structured questionnaire containing 40 items (available on request). This questionnaire was developed with the help of the national self-help group for patients receiving oral anticoagulation. The members of the patients' self-help group formulated sentences describing their feelings with regard to their treatment, of which 40 were combined into a questionnaire. Thereafter, the study patients estimated the impact of every item on their self-perceived treatment-related quality of life by a graded scale ranging from a minimum of 1 (total disagreement) to a maximum of 6 (total agreement). The 40 items covered 5 treatment-related topics: general treatment satisfaction, self-efficacy, strained social network, daily hassles, and distress. For every topic the total score was divided by the number of items included, resulting in a minimum score of 1 and a maximum of 6 for every topic, and the internal reliability coefficient of the questionnaire (Cronbach α) was assessed according to the method of Todd and Bradley.¹³ The person scoring the quality-of-life measures (Ms Steinhoff) was blinded to the treatment arm. The occurrence of all thrombotic and bleeding complications was recorded. Bleeding complications were classified as minor or major according to the criteria of Landefeld et al.¹⁴

Analysis

The data are presented as means and SDs or proportions. For comparison of groups, the Wilcoxon rank sum test (continuous variables) and 2-tailed Fisher exact test for categorical data were used. The proportions of patients with INR values within the target range during the follow-up time (2 time points) were additionally analyzed by means of repeated measurement analysis of variance for categorical data.¹⁵ This general methodology for multivariate categorical data obtained from repeated measurement experiments makes it possible to analyze the proportions of the 2 examina-

tions simultaneously by specifying group, time, and group-time interaction effects. The 95% confidence intervals (CIs) for means and risk ratios (RRs) were calculated by applying standard methods. The evaluation was performed on an intention-to-treat basis. For computations, SAS procedures (MEANS, FREQ, NPAR1WAY, and CATMOD) were used.¹⁶ $P < .05$ was regarded as significant.

RESULTS

From the 179 patients who were enrolled into the study, 90 patients were randomized to the self-management group and 89 to the control group (Figure, TABLE 1). A total of 165 patients were followed up for 6 months, 83 in the self-management group and 82 in the routine care group. Fourteen patients left the study without any follow-up examination and were excluded since no INR follow-up data were available for them. Five patients in the self-management group and 6 patients in the routine care group refused to participate in the follow-up examinations, 2 patients (1 in each group) died due to cardiac causes (heart failure and ventricular fibrillation), and anticoagulation was terminated in 1 patient when atrial fibrillation had permanently changed to sinus rhythm. After participation in the teaching and treatment program, 2 patients from the self-monitoring group did not perform anticoagulation self-monitoring at all. After randomization to the routine care group, 7 patients decided to participate in self-monitoring training and reported self-management of anticoagulation at follow-up. The evaluation of the study results was performed on an intention-to-treat basis; hence, these 9 patients remained in their original treatment groups.

During the follow-up period, 1 event of major bleeding occurred in each group. Twelve minor bleeding complications occurred in the self-management group and 10 in the routine care group. Two major nonfatal thromboembolic complications occurred (myocardial infarction and ischemic stroke), both in the routine care group. One patient

in the self-management group reported a transient (1 day) weakness of 1 leg, which might have been due to a minor cerebral ischemic episode.

Outcomes

At baseline, the groups did not differ significantly with regard to the squared INR value deviation from the mean of the individual INR target range or the percentage of patients within the target range (TABLE 2). The mean of the squared INR

value deviation at both follow-up examinations was significantly lower in the self-management group (Table 2). The INR values at the baseline examination were within the target range in less than 29% of the patients randomized to the self-management group (Table 2). At the 3- and 6-month follow-up this number increased to 57% and 53%, respectively, whereas the percentage of controlled patients in the routine care group did not change between baseline and 3-month

follow-up, but increased slightly thereafter (Table 2). In repeated measurement analysis for categorical data,¹⁵ the 2 groups differed significantly (χ^2 , 7.44; $P = .006$) concerning the probability of having INR values within the target range during the follow-up period (2 time points) adjusted for center (χ^2 , 34.39; $P < .001$) and time (χ^2 , 2.64; $P = .10$) effect. In this model only the main effects were used because all interactions (including the group-center interaction) were not significant. The larger proportion of patients with INR values within the therapeutic range in the self-management group was mostly due to a lower percentage of INR values that were too low (Table 2). At baseline, both groups were comparable with regard to the INR values. When controlling for the center effect using the Mantel-Haenszel analysis, the routine care group was more likely to be outside the target range at the 3-month follow-up (RR, 1.5; 95% CI, 1.2-2.0) but not significantly so at the 6-month follow-up (RR, 1.2; 95% CI, 0.9-1.6). In the intervention group, the number of patients with INR values above 4.5 decreased from 4 at baseline to 1 at 3 months and to 2 at 6 months. In the control group, INR values above 4.5 were present in 1, 2, and 1 patient, respectively. There were significant differences in the outcome parameter between the centers, so the center effect was included in the repeated measurement analysis. Since no interactions were significant, the final model contained only main effects. The center effect was significant, but the result of the group effect remained unchanged after including the center effect.

Patient Questionnaire

The treatment-related questionnaire was completed by 160 patients both at baseline and at 6-month follow-up. The internal reliability was acceptable as indicated by the Cronbach α values (TABLE 3). General treatment satisfaction and daily hassles scores improved in the self-management group and remained unchanged in the routine care group. The scores of self-efficacy and dis-

Table 1. Baseline Characteristics of Patients Who Were Randomized to the Control Group (Routine Care) and the Intervention Group (Self-management)

Variable	Routine Care Group (n = 89)	Self-management Group (n = 90)
Sex, No.		
Men	62	64
Women	27	26
Age, mean (SD), y	55 (12)	55 (12)
Weight, mean (SD), kg	77 (16)	74 (10)
Smoking status, No.		
Smoker	7	8
Ex-smoker	42	44
Nonsmoker	40	38
Heart valve replacement, No.	72	79
Atrial fibrillation, No.	6	3
History of minor bleeding, No.	10	10
History of major bleeding, No.	1	1
Duration of prior anticoagulant use, mean (SD), y	2.03 (4.78)	2.06 (4.77)
Phenprocoumon dosage, mean (SD), mg/wk	17.8 (6.8)	18.7 (5.6)

Table 2. Quality of Anticoagulation Control in the Control Group (Routine Care) and the Intervention Group (Self-management)*

Parameter	Routine Care Group	Self-management Group	P Value
Baseline (n = 179)			
Squared INR deviation, mean (SD)	1.00 (1.12)	1.32 (1.68)	.33
Within target range	36.4	28.9	.34
Below target range	53.4	61.1	.36
Above target range	10.2	10.0	>.99
3-Month Follow-up (n = 153)			
Squared INR deviation, mean (SD)	0.95 (0.96)	0.59 (1.21)	<.001
Within target range	33.8	57.0	.006
Below target range	50.0	32.9	.03
Above target range	16.2	10.1	.34
6-Month Follow-up (n = 164)			
Squared INR deviation, mean (SD)	0.83 (0.95)	0.65 (1.04)	.03
Within target range	43.2	53.0	.22
Below target range	48.2	33.7	.08
Above target range	8.6	13.3	.45

*INR indicates international normalized ratio. The quality of control is described as the mean squared deviation between the laboratory INR values and the individual INR target range (see "Methods" section), and as proportions of patients within, below, and above the initial INR target range at baseline, at the 3-month, and at the 6-month follow-up examinations. All data are presented as percentages unless noted otherwise.

tress improved in both groups, but improved significantly more in the self-management group (Table 3). The general treatment satisfaction scores displayed the most pronounced improvement. The intervention had no significant effect on the strained social network scores.

COMMENT

The results of this prospective randomized intervention study indicate that patients' self-management of oral anticoagulation based on a structured teaching and INR value self-monitoring program is safe and results in an improvement of both accuracy of anticoagulation control and treatment-related quality of life. The ability of patients to reliably measure their INR values has previously been convincingly documented.^{10,14,17-20} The recent development of a simpler device for self-monitoring of anticoagulation using blood obtained by finger pricking has facilitated patient acceptance.¹⁴ In this study, only 2 patients randomized to the intervention group did not want to perform self-monitoring throughout the study. Seven patients from the control group who originally agreed to continue without anticoagulation self-management for the 6-month duration of the study opted for this form of self-treatment outside of the study protocol.

We assessed 3 laboratory INR values in each patient in a blinded fashion. Based on this evaluation, the probability of the laboratory INR value at follow-up being within the therapeutic target range

was significantly higher in the intervention group. This was mainly due to a lower frequency of INR values below the target level of anticoagulation. A possible explanation could be that patients performing self-monitoring adjust the anticoagulant dosage whenever necessary more adequately compared with the routine physician care. Other factors in the intervention group, such as more frequent monitoring and the patient education program, may also contribute to this difference. Outcomes also improved in the control group, possibly because at baseline and at the 3-month follow-up, the control group patients were advised with regard to improving their anticoagulation control. Hence, the somewhat smaller difference between the study groups at the 6-month follow-up did not occur because of a loss of the beneficial effect in the intervention group, but rather was due to an improvement in the control group.

About two thirds of patients had INR values outside the target range at baseline. This level of anticoagulation control has been documented elsewhere,²¹ but other studies using different definitions have reported the proportion of patients with poor anticoagulation control to be about one third.²²⁻²⁴ The relatively high number of patients with poor control initially may have been caused by a rather high percentage of patients with relatively recent anticoagulation²⁵ and/or relatively narrow INR ranges in some cases. In this study, 138 patients had had anticoagulation less than 2 years and 105 had an INR target range

below 1.1; of these patients 70% and 71% had INR values outside the target range at baseline compared with 62% and 61% of patients with a longer anticoagulation duration and a wider INR target range, respectively.

Whether self-monitoring of anticoagulation resulted in the intervention effect or the effect was due to other components of the program cannot be determined from this study. However, we believe that proper self-management of oral anticoagulation should not be done without self-monitoring and a structured extensive teaching program.

This study was too small and too short to assess the effect of self-management on bleeding and thromboembolic complications. However, since this form of anticoagulation therapy results in a lower frequency of suboptimal anticoagulation values without increasing the rate of excessive values, we expect that thromboembolic complications would be reduced in a larger, longer study.

We estimate the total cost of self-monitoring 1 INR value to be about 9 European Currency Unit (ECU) (≅\$11 US). This calculation is based on the costs over a 5-year period of 1 patient enrolling in a structured teaching and treatment program (150 ECU), 1 CoaguChek device (1030 ECU), 52 test strips per year (180 ECU), 52 lancets per year (7 ECU), and 4 control solutions per year (1.5 ECU). In Germany, patients taking oral anticoagulation therapy are usually advised to visit a physician for control of the INR values twice a month. The estimated mean cost for such a visit is 16 ECU.

Table 3. Assessment of Treatment-Related Quality-of-Life Scores at Baseline and at the 6-Month Follow-up in the Routine Care Group and the Self-management Group*

Variable	Baseline			Follow-up			Difference Between Baseline and Follow-up		P Value
	Cronbach α	Routine Care	Self-management	Cronbach α	Routine Care	Self-management	Routine Care	Self-management	
General treatment satisfaction	0.79	2.90 (1.38)	2.69 (1.47)	0.85	2.96 (1.58)	4.21 (0.82)	+0.24 (1.48)	+1.54 (1.38)	<.001
Self-efficacy	0.64	4.72 (1.00)	4.61 (0.94)	0.64	5.11 (0.85)	5.47 (0.63)	+0.35 (0.96)	+0.83 (0.92)	.003
Strained social network	0.82	2.23 (1.04)	2.26 (1.02)	0.77	2.00 (0.95)	1.82 (0.79)	-0.23 (0.79)	-0.40 (0.83)	.19
Daily hassles	0.66	2.10 (0.75)	2.34 (0.84)	0.66	2.07 (0.69)	1.96 (0.79)	-0.03 (0.53)	-0.49 (0.83)	.01
Distress	0.78	2.91 (1.12)	3.09 (1.12)	0.78	2.72 (1.16)	2.55 (1.08)	-0.21 (0.93)	-0.61 (0.87)	.008

*Routine care and self-management values are listed as mean (SD). Evaluation was based on a structured questionnaire containing 40 items covering 5 treatment-related topics: general treatment satisfaction, self-efficacy, strained social network, daily hassles, and distress. Maximum score was 6 and minimum score was 1. Internal reliability is indicated by Cronbach α.¹³

Therefore, even by only reducing the outpatient visits by 50% to once a month (in patients performing INR self-monitoring) this form of therapy will be cost-effective. However, a comprehensive evaluation of the cost-effectiveness has to include the costs of thromboembolic and bleeding complications. Since this was not in the scope of this study, a full evaluation must be left to larger investigations aimed at reducing the clinical end points.

Patients receiving oral anticoagulation therapy often worry about complications, dietary limitations, less freedom when traveling, frequent and sometimes difficult venous punctures, and regular visits to physicians and laboratories. These factors are likely to decrease quality of life. In this study we have

shown that when anticoagulant therapy is based on self-monitoring and self-management, most aspects of treatment-related quality of life do improve. In addition, when patients travel, INR values are determined by a variety of laboratories, and differences due to the reagents and clot timers may be important²⁰ and result in unwarranted changes of therapy. Therefore, INR self-monitoring has the additional advantage of consistency of testing performed by a single system.

In conclusion, self-management of oral anticoagulation can be performed by patients, can improve patients' reported treatment-related quality of life, and may potentially improve medical outcomes. Larger studies with longer follow-up are needed to determine the efficacy of this form of therapy in reduc-

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