Self-management of warfarin therapy

BACKGROUND Clinical studies from other countries show that self-management of warfarin therapy may reduce the risk of mortality, thromboembolism and complications when compared to conventional therapy. The purpose of this study was to train patients in self-management and compare the results with conventional therapy in Norway.

METHOD A total of 23 patients who had previously been given conventional therapy by their GPs were instructed in how to measure INR (using the CoaguChek XS device) and administer warfarin dosage through a structured training programme over the course of 27 weeks. The participants continued with self-management for a further 28 weeks after the end of the training period. The time in the therapeutic range (TTR, measured as a percentage) was calculated and the TTR for conventional therapy and self-management were compared.

RESULTS No significant difference in average TTR was found when comparing conventional therapy (70 % (95 % confidence interval (CI) 62–78)) with the self-management period (75 % (95 % CI 69–81, p = 0.24)). The percentage of extreme INR values (< 1.5 or > 5.0) was higher during conventional therapy than during self-management (6.8 % vs. 1.0 %, p < 0.001).

INTERPRETATION No significant difference in TTR was found when comparing self-management and conventional warfarin therapy in our study, but for self-management there was a lower percentage of extreme INR values compared to conventional warfarin therapy.

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In 2013, around 87 000 patients were treated with warfarin in Norway, and an increasing number of patients are being treated with anticoagulants in general (2). Direct oral anticoagulants such as dabigatran, rivaroxaban and apixaban will probably replace warfarin for some patients in the future (2). However, warfarin is still the only approved anticoagulant for patients with mechanical heart valves (3). Moreover, there is a lack of evidence to support the use of direct oral anticoagulants in some other indications for warfarin, and they are either contraindicated or must be used with caution in certain patient groups (4–6).

For most patients in Norway, conventional warfarin therapy entails a trip to their GP to have samples taken for INR measurement and an appropriate dose of warfarin prescribed. The INR is usually analysed every 4–6 weeks. Alternatives to conventional therapy are self-testing (patient measures INR, doctor decides warfarin dose) or self-management (patient measures INR and decides warfarin dose). During self-management, the INR is typically measured once per week. In 2008 there were approximately 250 000 individuals worldwide who performed self-management (7). To the best of our knowledge, there are no more recent data available, but Roche state that as of 2012 they had sold around 300 000 devices for self-testing/self-management (Roche Diagnostics Norway, personal communication). Self-management has long been in demand in Norway (8), and doctors can now apply to the agencies responsible for medical aids for reimbursement of expenditure on self-testing devices and strips for their patients (9, 10). However, there are no funds allocated to training in INR measurement and warfarin dosing, which is very important for self-management (11).

Meta-analyses show that self-management can reduce the risk of death, thromboembolism and serious complications compared with conventional therapy (12, 13). Given that such outcomes are rare during warfarin therapy, large numbers of patients are required in order to compare these types of events (14). Time in the therapeutic range (TTR, measured as a percentage) is therefore recommended as a surrogate measure or secondary endpoint for the efficacy of anticoagulation therapy (14), and meta-analyses have shown that TTR during self-management is equal to or greater than that seen with conventional therapy (12, 15). Self-management is also the most cost-effective method (16). Because TTR and the efficacy of conventional anticoagulation therapy vary between countries (17), and because methods used to train patients in self-management may differ (18), it is difficult to extrapolate existing results directly to Norway. The purpose of this study was thus to test a training programme for self-management of warfarin therapy and then compare the results from this programme with those of conventional therapy in Norway.

Material and methods

Recruitment of patients

Patients on long-term or lifelong warfarin therapy were enrolled in the study in the period June to August 2008. Ten GP surge-

MAIN MESSAGE

This is the first study in Norway to compare self-management of warfarin therapy with conventional warfarin therapy

There was no significant difference in time in the therapeutic range with conventional therapy versus self-management

The proportion of extreme values (sub- and supratherapeutic INR) was lower with self-management than with conventional therapy

Table 1 Patient characteristics

Number (N)	24
Excluded (n) (%)	1 (4)
Female (n) (%)	9 (38)
Average age (lowest–highest) (years)	55 (35–69)
Indication for warfarin therapy (n) (%)	
Venous thromboembolism	14 (58)
Atrial fibrillation	7 (29)
Artificial heart valve	3 (13)
Average duration of warfarin therapy prior to study (lowest–highest) (years)	7.6 (0.3–25)
INR target values (therapeutic range) (n) (%)	
2.5 (2.0–3.0)	21 (88)
3.0 (2.5–3.5)	3 (12)
Total number of events during conventional warfarin therapy (n) (%)	8 (33)
Number of patients with thromboembolic events	4 (17)
Number of patients with major haemorrhage (with hospital admittance)	1 (4)
Cases of minor haemorrhage (without hospital admittance)	3 (13)
Total number of events during training and self-management (n)	0

ries in Bergen were informed about the study, and the GPs were asked if they could arrange contact with appropriate patients. Further individuals were recruited through an advertisement in the newspaper Bergens Tidende. Those who wished to take part got in touch by telephone and were added to a continuously updated list. Power calculations showed that ten INR values from conventional therapy and self-management would be needed for a minimum of 20 patients in order to detect a 10 % change in TTR (see data collection and statistics). Therefore, the first 24 of the more than 100 persons who signed up and who fulfilled the inclusion criteria were enrolled. Although a total of 24 patients were recruited, one patient stopped taking warfarin during the study period and was therefore excluded. The 23 patients who received training in self-management also made up the conventional therapy group. Only patients aged 18–70 were invited to participate in the study, and the GP of each patient assessed his/her suitability for self-management of warfarin therapy. Patients had to be able and motivated to follow the training programme and to ultimately take responsibility for their own warfarin therapy. The conventional part of the treatment consisted of the period before the patients were included in the study (39 weeks), during which they were monitored by their GP.

The study was approved by the Regional Committee for Medical and Health Research Ethics, Western Norway and the Norwegian Social Science Data Services. Patients were given information about the study verbally and in writing, and were included after providing verbal and written consent. Patient characteristics are shown in Table 1.

The study aims have remained unchanged from study initiation through to publication of data. The study was not registered as a clinical trial in a publicly available registry when enrolment of patients began in June 2008. We did not consider the study to involve a direct medical intervention in patients as defined in the guidelines of the International Committee of Medical Journal Editors (ICMJE) 2004 (19). The patients' treatment was not changed, but the INR was measured more frequently and patients were more closely monitored. The study has been retrospectively registered at ClinicalTrials.gov (registration number NCT02371772).

Training programme

In this longitudinal study, patients underwent a 27-week training programme (after 39 weeks of conventional therapy) which, upon completion, should enable them to self-manage their warfarin therapy. The training programme was developed by Aarhus University Hospital in Denmark (20, 21) and follows international guidelines (11). Four biomedical laboratory technologists, a doctor and a scientist from the Norwegian Quality Improvement of Primary Health Care Laboratories (Noklus) and the University of Bergen were involved in the preparation of training materials and training of patients. One of the biomedical laboratory scientists was responsible for day-to-day contact with and the follow-up of patients. The training programme is divided into three periods (Table 2), each of which began with a three-hour course. In the first of these evening sessions, the doctor went through topics including the medical basis of warfarin therapy and the various factors that can affect INR values, and training was provided in use of the INR device. Throughout the first period, participants measured their INR with the CoaguChek XS every day in order to practice carrying out the measurement itself, but dose adjustment was performed only once a week (Table 2). Decisions regarding warfarin dose were made by the biomedical laboratory scientist in consultation with a doctor on the basis of weekly results obtained with hospital instruments. In the second evening session, the doctor outlined the principles behind warfarin dosing, and various causes of fluctuating INR values were discussed. The guidance given to patients regarding dosage followed the recommendations of The Norwegian Medical Association (22). In the third evening session, participants exchanged experiences and worked under supervision on group assignments related to the training.

After 27 weeks, the participants took a final written test which they had to pass before being allowed to continue self-management for a further 28 weeks (Table 2). During the training and self-management periods, participants could contact the biomedical laboratory scientists by email or telephone during the day if they had questions or were unsure about the analysis or dosage. They were instructed to contact the Accident & Emergency department or hospital in the event of acute problems. Responsibility for anticoagulation therapy was transferred back to the GP at the end of the study.

INR instruments

CoaguChek XS (Roche Diagnostics, Switzerland) is a small, handheld device for the self-testing of INR. The device shows good analytic performance (23) and is easy for patients to use after thorough training (24). Capillary blood from the finger is applied to a test strip placed in the device for analysis of the INR. The reagents SPA50 (used from 25 August 2008 to 18 January 2009) and SPA+ (used from 19 January 2009 to 23 February 2009) (Stago, France) were used for analysis of INR in patient plasma in the

Table 2 Schematic overview of the training programme[1] and self-management period

	Training in self-management					Self-management
	Period 1 (weeks 1–3)		Period 2 (weeks 4–12)	Period 3 (weeks 13–27)		(weeks 28–55)
INR-measurement at home	Daily		Weekly	Weekly		Weekly
Dose adjustment	Biomedical laboratory scientist/doctor decides warfarin dose weekly (3 weeks)		Patient suggests warfarin dose. Biomedical laboratory scientist/doctor approves/ adjusts dose (9 weeks)	Patient decides warfarin dose. Biomedical laboratory scientist/doctor checks dose every 4th week (15 weeks)		Patient decides warfarin dose (28 weeks)
Parallel analysis Comparison of own INR-result with INR-result from hospital device	Weekly		Every 3rd week	Every 4th week		None
Course/exam	Week 1: Course	Week 3: Assessment of measurement technique	Week 4: Course	Week 13: Course	Week 27: Written exam	

[1] Modified from Hasenkam et al. (20) and Christensen et al. (21)

hospital instrument, STA-R Evolution (Stago, France). Recommended procedures for internal and external controls (25) were followed, and gave acceptable results.

Results from this parallel analysis showed that any inconsistencies between the Coagu-Chek XS and STA-R Evolution during the training period were within the acceptable limits set out in the ISO standards for self-testing devices (26).

Data collection and statistics

In the conventional therapy period (39 weeks), during which patients were monitored by their GP, the last ten INR values before study entry for each patient were obtained, as well as details of any complications experienced while on warfarin. These data were obtained from the GP and/or the INR patient card. All INR values and daily warfarin doses during the training and self-management periods were recorded, and patients were told to report any complications. Data were collected from August 2008 to September 2009 and were recorded and analysed using Microsoft Excel 2007 and SPSS PASW version 18 for Windows. Statistical outliers were excluded in accordance with Burnett (27). During the training period, warfarin therapy was temporarily discontinued for one patient because of surgery, and INR values were excluded for the period from and including the discontinuation, up to and including ten days after warfarin reintroduction.

A chi-square test was performed to examine whether the proportion of extreme INR values differed between the various periods. Death, thromboembolic events and serious complications are relatively uncommon during warfarin therapy, and a large number of patients are therefore needed in order to compare these types of events (14). The reduction in the risk of adverse clinical events with increasing TTR is well documented (14, 17, 28). TTR was therefore used as a surrogate measure of the efficacy of anticoagulation therapy, as recommended (14), and calculated as described by Rosendaal and co-workers (29). In this method it is assumed that any given change between two measurements is linear, and TTR is defined as the number of patient days with INR values in the therapeutic range divided by the total number of patient days. Paired t-tests and F-tests were used to test for differences in median TTR and TTR variation (standard deviation, SD) respectively, between the three periods; $p \leq 0.05$ was considered to be statistically significant.

Results

All patients (n = 23) completed the training programme, passed a practical and written examination and completed 28 weeks of self-management.

Mean TTR increased from 70 % (95 % confidence interval (CI) 62–78) with conventional therapy to 82 % (95 % CI 78–86) in the training period ($p = 0.005$), and was still higher in the self-management period (75 % (95 % CI 69–81)), although it was no longer significantly different from conventional therapy ($p = 0.24$) (Figure 1, Table 3). There was significantly less variation in TTR during self-management (SD 13 %) than during conventional therapy (SD 19 %) ($p < 0.05$). The conventional therapy period was 39 weeks long (10^{th}–90^{th} percentile 23–60) with approximately ten INR measurements reported per patient (Table 3). The self-management period was 28 weeks long with 28 INR measurements (10^{th}–90^{th} percentile 24–31) per patient. The number of days between INR measurements, and the INR values, are shown in Table 3. During conventional therapy, 6.8 % of recorded INR values were extreme values compared with 1 % during training and self-management ($p < 0.001$). With conventional therapy, there were 12 low (INR < 1.5) and four high (INR > 5.0) extreme values, whereas with self-management, there were five low extreme values and one high. Eight complications were recorded among the participants prior to enrolment (over an average of 7.6 years), and none in the course of the study (28 weeks) (Table 1).

Discussion

A total of 23 patients were trained in self-management of warfarin therapy. There was no statistically significant difference in TTR with conventional therapy (70 %) versus self-management (75 %) (Figure 1). However, variation in TTR (Figure 1) and the percentage of INR extreme values (Table 3) were both significantly reduced with self-management compared to conventional therapy. Given the large differences in duration and relatively small number of participants, it is not possible to draw any conclusions about whether conventional therapy and self-management differ with regard to complications.

Our findings concur with the results of meta-analyses, which have shown that TTR during self-management is equal to or greater than that achieved with conventional therapy (12, 15). During self-management, the INR was analysed more frequently than with

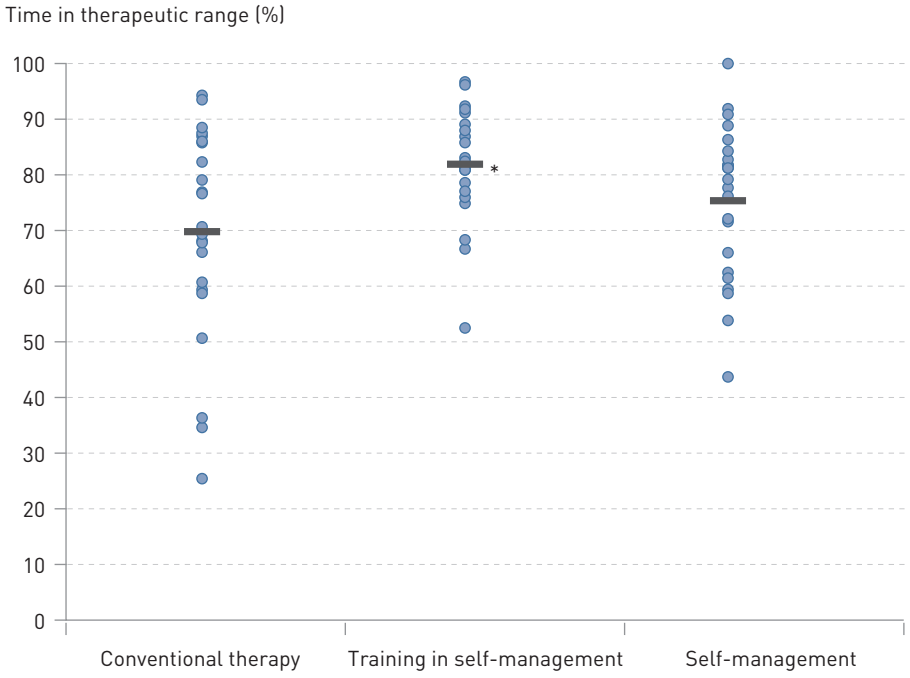

Figure 1 *Time in the therapeutic range (TTR) for each patient for the three periods of the study (conventional therapy, training in self-management, and self-management). Time in therapeutic range = number of patient days with INR values in the therapeutic range divided by the total number of patient days. Horizontal lines indicate the mean TTR. *p = 0.005 compared with conventional therapy. There was no statistically significant difference between TTR with self-management versus conventional therapy (p = 0.24)*

conventional therapy (Table 3). This means that values outside the therapeutic range are detected more quickly, which probably leads to more rapid adjustment of warfarin dose (14), which in turn increases TTR. Indeed, it has been shown that an increased frequency of INR measurements leads to increased TTR (30, 31). This may explain why the proportion of INR extreme values (Table 3) and the variation in TTR (Figure 1) were lower during self-management than with conventional therapy, in common with previous meta-analyses (13). Increased INR variation has been shown to correlate with an increased incidence of death, stroke and bleeding (32).

An important aspect of self-management is that patients become more knowledgeable about and more involved with their own treatment. This presumably leads to a more positive attitude towards treatment in these patients compared to those who have not received such training. This may also contribute to increased compliance (33).

To verify CoaguChek XS measurements during the training period, blood samples were collected for measurement of the INR using hospital instruments (parallel analysis, Table 2). Organisations including the International Organization for Standardization (34) and the Clinical and Laboratory Standards Institute (35) recommend that patients who self-test should participate in an external quality assurance programme. Among the external quality control organisations in Europe, as yet only «External quality Control of diagnostic Assays and Tests» (ECAT) in the Netherlands offers such a programme for patients who perform INR self-testing (36). Germany has chosen not to offer this service because of a lack of capacity resulting from large patient numbers, and because the control sample material has not been adequate (37). However, new control materials have entered the market, and Noklus is planning a study to test different models of external quality control for self-testing devices. Currently, Noklus recommends that patients have their device checked twice a year at their GP surgery.

A strength of this study is that the same patients underwent both conventional therapy and self-management, thus the patients can act as their own controls. In addition, all enrolled patients completed the entire study. A weakness is that there were relatively few patients compared with large international studies, but nonetheless enough to be able to demonstrate a 10 % change in TTR, as recommended (14). As more Norwegian patients undergo training, more robust data will be obtained.

Table 3 INR-measurements and time in the therapeutic range with conventional therapy, during training in self-management and with self-management

	Conventional therapy (39 weeks[1])	Training in self-management (27 weeks)	Self-management (28 weeks)
Number of INR-measurements per patient (median) (10^{th}–90^{th}-percentile)	10 (8–12)	45 (42–55)	28 (24–31)
Number of days between INR-measurements for each patient (median) (10^{th}–90^{th} percentile)	27 (17–62)	3.1 (2.4–3.4)	6.0 (5.8–7.3)
INR-value (median) (10^{th}–90^{th} percentile):			
Therapeutic range 2.0–3.0 (n = 20)	2.4 (1.7–3.3)	2.5 (2.0–3.3)	2.6 (2.0–3.3)
Therapeutic range 2.5–3.5 (n = 3)	2.7 (1.7–3.4)	2.7 (2.2–3.5)	2.9 (2.4–3.4)
Lowest/highest INR-value	0.8/7.1	1.3/5.5	1.2/5.2
Extreme values (INR < 1.5 or INR > 5.0) (%) (number)	6.8 (16)	1.0 (10)[2]	1.0 (6)[2]
Time in the therapeutic range (%) (95 % CI)	70 (62–78)	82 (78–86)	75 (69–81)

[1] Median (10^{th}–90^{th}-percentile 23–60 weeks)

[2] p < 0.001 compared with conventional therapy. There was no significant difference in extreme values between training in self-management and self-management

Patients were selected on the basis that they wished to begin self-management, and were considered suitable for self-management by their GP. This means that the patients in this study are a selected group, and the results are therefore not representative of all patients on anticoagulation treatment. Selection of patients is, however, a recommended and common practice in clinical trials (11–13).

Patients provided written feedback after each evening training session and at the end of the study. They were generally very satisfied with the training programme and follow-up (1). On the basis of the evaluations, the training programme was revised and shortened to 21 weeks. This programme is now being used to train patients in ten health authorities in Norway (38, 39), with training paid for by the hospitals. Although direct oral anticoagulants are expected to replace warfarin for a large proportion of patients with atrial fibrillation in the future, warfarin will remain the first choice for many others, including those with an artificial heart valve. If this standardised training programme were implemented in all health authorities, all suitable patients on long-term warfarin therapy could have equal access to self-management irrespective of their geographical location. It is puzzling that the Norwegian government earmarked NOK 87 million for direct oral anticoagulants in 2013 (40), whereas no funds have been allocated to training patients in self-management of warfarin.

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