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Quality of Warfarin Therapy and Quality of Life are Improved by Self-Management for Two Years

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Abstract

Background Studies from several countries show that self-management of vitamin K antagonist (e.g., warfarin) therapy reduce the risk of complications compared with conventional management.

Objectives The aim of this study was to investigate the quality of warfarin management when patients were transferred from conventional management to self-management in Norway. In addition, quality of life (QoL) before and after 2 years of warfarin self-management was investigated.

Materials and Methods The study was longitudinal with a retrospective and prospective design where 126 patients on conventional management of long-term warfarin therapy underwent a 21-week training program of warfarin self-management followed by 2 years of self-management. The outcomes of the study were time in therapeutic range (TTR), the variance of international normalized ratio (INR) values, extreme INR values (INR $\leq$ 1.5 and $\geq$ 5), complications, and QoL, comparing the 2-year period of the conventional management with the 2-year period with the self-management.

Results The median TTR was higher during self-management compared with conventional management (78.1% vs. 65.9%, respectively, $p < 0.001$). In addition, self-management resulted in lower INR variance (0.22 vs. 0.33, $p < 0.001$), reduced percentage of extreme INR values (1.8% vs. 5.3%, $p < 0.001$), less complications (0% vs. 5.6%), and improved QoL ($p < 0.001$) compared with conventional management.

Conclusion We used five different measures and found improved quality of warfarin self-management 2 years after patients were transferred from the conventional management.

Keywords
- international normalized ratio
- quality of life
- self-management
- time in therapeutic range
- warfarin

Introduction

Oral anticoagulant therapy (OAT) is indicated for both prophylactic and therapeutic use in patients with increased risk of thromboembolism.[1] The vitamin K antagonists (VKAs) (e.g., warfarin) has been the main OAT for more than 60 years, but after approval of the direct oral anticoagulants (DOACs; dabigatran etexilate, rivaroxaban, apixaban, and edoxaban), the use of VKAs has been decreasing.[2] However, DOACs are contraindicated in, for example, patients with

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mechanical heart valve,[3] with severely reduced renal function, and with antiphospholipid syndrome.[4] Also, use of DOACs in the elderly has been of concern because of comorbidity, drug–drug interactions, and decreased drug clearance.[5] In Norway, approximately 43,000 patients (1% of the population) used warfarin and 115,500 patients (2% of the population) used DOACs in 2018.[6]

Patient self-management (PSM) of VKA therapy is a concept empowering the patients by enabling trained patients to monitor and adjust their management in a home setting. Meta-analysis from randomized clinical trials show that PSM of VKA therapy reduces the risk for complications compared with conventional management.[7,8] A cohort study from clinical practice in Denmark, with 5 years of follow-up, also found a reduction especially in bleeding events, but also in thromboembolic events and deaths in patients with mechanical heart valve performing PSM compared with conventional management.[9] In addition, a Cochrane review has demonstrated that quality of life (QoL) during PSM increases compared with conventional management.[8] Complications like thromboembolism, bleeding, and death are decreased during VKA management,[1] and are used as primary outcomes in larger trials. However, when the length of the study as well as the number of patients are limited, time in therapeutic range (TTR) is recommended as outcome for anticoagulant management.[10] Meta-analysis show that TTR during PSM is equal to or higher than that seen with conventional management.[7,11] However, none of the studies included in the meta-analysis have been performed in Norway. Since the quality of conventional VKA management varies in different countries,[12] and methods used to train patients in self-management may differ,[13] it is important to compare PSM with conventional management in each country. It must be emphasized that PSM is an option only for a selected group of patients.[14] The estimates of suitability vary between 10 and 80% of the patients[8,13] due to different criteria for eligibility and indications for VKA management.[15] In a previous pilot study performed in Norway, a training program for PSM of VKA therapy was tested, and was the first study in Norway where results from PSM were compared with conventional VKA therapy.[16,17] For the 23 included patients there were no difference in TTR when comparing conventional management (39 weeks) with self-management (23 weeks). In 2018, approximately 1,350 patients had attended a revised version of this training program which was originally developed at Aarhus University Hospital (Denmark)[18] and modified by the Norwegian Organization of Quality Improvement of Laboratory Examinations (Noklus).[17] In Norway, the quality of the conventional VKA management is relatively good (TTR: ~70%),[12] and therefore of interest to explore, in a larger study, if PSM could increase the quality even further. Thus, the aim of this study was to investigate the quality of VKA therapy, using four different outcomes, when patients are transferred from conventional management to self-management in Norway. In addition, we investigated the QoL before and after 2 years with PSM of warfarin therapy.

Materials and Methods

Study Design

The study was longitudinal with a retrospective and prospective design where the same patients constituted the conventional and self-management group. All patients started warfarin treatment in the conventional group, and after the training in PSM, all patients were transferred to the self-management group.

Study Population

Patients on long-term/life-long warfarin therapy were recruited from December 2010 at general practitioners' (GP) offices and cardiac outpatient clinics in Tromsø and Bodø (Norway). A letter with information about the project was sent to all GP offices (~220), asking for patients that could be suitable for the study. Also, the health care professionals at the GP offices were informed about the project so that they could inform eligible patients. Since there was a low response from the GPs in Tromsø, there was an advertisement in a local newspaper and at a Web page for GPs collaborating with the Arctic University (University of Tromsø) of Norway. In addition, the physician responsible for the participants in Tromsø recruited patients from the outpatient clinic at the University Hospital of North Norway. The physician of each patient assessed her/his suitability for warfarin self-management. This included physical health, mental suitability, motivation, and expected level of compliance with PSM. Patients had to be between 18 and 70 years old. In addition, they had to have the ability and motivation to follow the training program and take responsibility for their own warfarin therapy. Exclusion criteria were drug abuse and hepatic disease. The goal was to recruit approximately 150 patients which was the economic and practical limit for the study. In addition, all the patients had to complete the training program in self-management of warfarin within 1 year. The GPs were in charge of warfarin dosing during the conventional management period. All participants gave written informed consent to participate in the study. The study was approved by the Regional Committee for Medical and Health Research Ethics, Western Norway (REK/ 2008/4873), and the project is registered at ClinicalTrials.gov (registration number NCT 02864537).

Study Intervention

All patients underwent a 21-week training program in self-management of warfarin therapy between March 2011 and February 2012 (►**Table 1**). The program follows international guidelines[14] and was originally developed at Aarhus University Hospital (Denmark)[18] and modified and tested in a Norwegian setting by Noklus.[17] The content of the training program has previously been described.[17] In short, the first period started with a 3-hour course where basic knowledge of warfarin therapy and international normalized ratio (INR) was the main focus, in addition to instructions and practice in the use of the handheld point-of-care (POC) INR instrument (CoaguChek XS [Roche Diagnostics, Switzerland]). For 2 weeks the participants themselves measured their INR

Table 1 Schematic overview of the training program[a] and self-management period

	Training in self-management						Self-management
	Period 1 (weeks 1–2)		Period 2 (weeks 3–9)		Period 3 (weeks 10–21)		2 years
INR measurement at home	Daily		Weekly		Weekly		Weekly
Dose adjustment	BLS/physician decides warfarin dose weekly (2 weeks)		Patient suggests warfarin dose. BLS /physician approves/adjusts dose (7 weeks)		Patient decides warfarin dose. BLS/physician checks dose every 4th week (12 weeks)		Patient decides warfarin dose
Split sample: Comparison of CoaguChek XS INR result with hospital INR result	Weekly (three measurements)		Every 3rd week		Every 4th week		Opening a new box with test strips
	Week 1:	Week 2:	Week 3:		Week 10:	Week 21:	
Course/test	Course		Course assessment of measurement technique		Course	Written test	

Abbreviation: BLS, biomedical laboratory scientist; INR, international normalized ratio.
[a]Modified from Hasenkam et al[18] and Sølvik et al.[17]

every day with their own INR device, but assessment of dose adjustment was performed only once a week based on weekly INR values analyzed on the hospital instrument. Decisions regarding warfarin dose were made by the responsible biomedical laboratory scientist (BLS) in consultation with a physician. The second period started with a course where the topics were warfarin dosing and fluctuation of INR values. The participants measured their INR once a week for 7 weeks and suggested their warfarin dose followed by approval/adjustment by the BLS/physician. In the third period, the participants decided the warfarin dose and the BLS/physician checked every 4th week. After a total of 21 weeks, the participants had to pass a written test to be allowed to continue self-management (►**Table 1**). The written test is theoretical/objective with questions regarding which practical aspects they must be aware of to perform a correct measurement of INR with the POC instrument. Furthermore, they are asked about how different food, medications, and life-style may affect their INR values. In addition, they have to answer how they will dose and when they will measure a new INR in the case of a specific INR deviation from their own therapeutic interval, and in the case they missed a warfarin dose. During the training and self-management periods, participants could contact the BLS by email or telephone during the day if they were hesitant about the INR analysis or warfarin dosage or had other questions related to the management. They were instructed to contact the emergency department or hospital in the event of symptoms/signs of emergencies (e.g., bleeding or thrombotic complications). The responsibility for the follow-up of the anticoagulation therapy was transferred back to the GP after the training period.

The INR Instrument Used

CoaguChek XS (Roche Diagnostics) is a small, handheld device for the self-testing of INR. The device shows good analytic performance[19] with an analytical variation (CVa) of approximately 3%[20] and is easy for patients to use after thorough training.[20] Capillary blood from the finger is applied to a test strip placed in the POC device for analysis of the INR. The reagents SPA50/SPA+ (Stago, France) were used for analysis of INR in citrated plasma on the hospital instruments, STA-R and StaR Evolution (Stago). Standard procedures for internal and external controls were followed, and gave acceptable results. Results from the split-sample analysis (comparison of CoaguChek XS INR result with hospital INR result) showed that the INR values during the training period were within the acceptable limits given by the International Organization for Standardization for self-testing devices[21] (►**Supplementary Fig. S1**, available in the online version).

Data Collection

The recommended therapeutic range and the INR values for each patient 2 years before enrolment (conventional management period), 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, therapeutic range, and daily warfarin doses reported during the training and self-management periods were recorded, and patients were told to report any complications. Data were collected from 2008 to 2013. At inclusion, each participant filled out a validated QoL questionnaire developed for patients on VKA.[22] The questionnaire consists of 32 items covering 5 management-related topics: general management satisfaction, self-efficacy, distress, daily hassles, and strained

social network. A graded scale ranging from a minimum of 1 (Doesn't apply) to maximum of 6 (Applies fully) is used. The questionnaire was translated to Norwegian in the pilot study and translated back to English to ensure that the translation had not changed the meaning of the questions.[16] The participants filled in the same questionnaire after 2 years of self-management.

Statistics

The outcome measures for the quality of warfarin treatment were TTR, INR variance ($\frac{\sum(x-\bar{x})^2}{n-1}$), percentage of extreme INR values (INR $\leq$ 1.5 and $\geq$ 5.0), and number of complications (thromboembolic events and major hemorrhage). The calculations of the outcomes were performed using data from 2 years or the maximum length of conventional management if this was less than 2 years ($n = 126$). Likewise for the data from the PSM period ($n = 126$). In total, 92% of the patients participated between 1.5 and 2 years both in the conventional management and the PSM period (►**Supplementary Table S1**, available in the online version). In addition, some variables were calculated from 0.5, 1, 1.5, and 2 years before enrolment (conventional management), during training in PSM, and after 0.5, 1, 1.5, and 2 years with PSM. The number of patients at each of these time points is shown in ►**Supplementary Table S2** (available in the online version). Thromboembolic events were defined as ischemic stroke or any form of thromboembolic events. Bleeding events were registered according to the International Society on Thrombosis and Haemostasis criteria.[23] Major bleeding events were those that lead to hospitalization, demanded blood transfusion, resulted in a fall in hemoglobin level of $\geq$ 2.0 g/dL, were intracranial, or resulted in death. Information about thromboembolic and bleeding events in the conventional management period were obtained from the patients' GP. TTR, defined as the number of patient days with INR values in the therapeutic range divided by the total number of patient days, was calculated as described by Rosendaal and colleagues.[24] In this method, it is assumed that any given change in INR between two measurements is linear. For each INR measurement, the number of days within therapeutic range since the last test was calculated and divided by the number of days since the last test. Finally, the sum of total number of days within therapeutic range was divided by the total number of days and multiplied by 100. Analysis of QoL was performed as described by Sawicki[22] at baseline before training and after 2 years of PSM. Baseline is defined as the point when the patients started the training in self-management. The difference in TTR between the two periods (conventional management and PSM) was normally distributed, and a paired *t*-test was used to test for differences in TTR. TTR, INR variance, percentages of extreme INR values, and QoL were not normally distributed, and therefore the Wilcoxon signed-rank test was used to compare these variables during conventional management and PSM, and QoL at baseline and after 2 years with PSM. The differences in all the parameters were calculated based on the same number of patients in both the conventional and PSM groups (TTR, INR variance, extreme INR values: $n = 126$, QoL: $n = 103$). A Spearman's correlation test was used to assess if there was a correlation between INR variance and TTR, between INR variance and the frequency of INR measurements, between TTR and the frequency of INR measurements, and between TTR and QoL. A *p*-value of $\leq$ 0.05 was considered to be statistically significant. Statistical analysis was performed using Microsoft Excel version 15.39 and SPSS PASW version 25 for Windows.

Results

In total, 132 patients were recruited. Six patients were excluded due to incomplete information about INR values from the conventional management period ($n = 3$), during training ($n = 1$), and/or during PSM ($n = 5$). For the remaining 126 patients included in the calculations, the characteristics at baseline are shown in ►**Table 2**. There were more men (69%) than women, and the median age was 59 years (10th–90th percentile 38–67). There was diversity in the therapeutic range among the patients, but every patient had the same therapeutic range during the conventional management and PSM periods

Table 2 Patient characteristics at baseline

Number (*N*)	126
Gender	
Female, *n* (%)	39 (31)
Male, *n* (%)	87 (69)
Age, median (10, 90 percentiles), years	58.9 (38.3, 67.3)
Indication for warfarin therapy, *n* (%)[a]	
Atrial fibrillation	33 (27)
Venous thromboembolism	32 (25)
Artificial heart valve	30 (24)
Arterial thromboembolism	18 (14)
Cannot be classified[b]	14 (11)
Duration of warfarin therapy prior to study, median (10, 90 percentiles), months	23.6 (7.2, 39.7)
INR target values (therapeutic range), *n* (%)[c]	
2.3 (2.0–2.5)	10 (7.9)
2.5 (2.0–3.0)	69 (55)
2.8 (2.5–3.0)	6 (4.8)
3.0 (2.5–3.5)	29 (23)
Other[d]	12 (9.5)

Abbreviation: INR, international normalized ratio.
[a]Four patients had more than one indication for warfarin therapy.
[b]Missing: $n = 2$ (1.6%), insufficient information to be classified: $n = 14$ (11%).
[c]The INR therapeutic range was decided by the general practitioners or hospital physician.
[d]Range: 2.0–3.5, 2.2–3.3, 2.5–4.0, 2.5–4.2, 2.6–3.4, 2.6–4.4, 2.8–3.5, 3.0–4.0, 3.0–3.5.

Table 3 Observation time, frequency of INR measurements, time in therapeutic range, INR variance and extreme INR values during conventional management and self-management

	Conventional management		Self-management		*p*-Value[a]
	($n = 126$)		($n = 126$)		
Observation time, median (10, 90 percentiles), months	23.6	(7.2, 24.8)	24.1	(13.4, 24.6)	0.081
Number of INR measurements per patient, median (10, 90 percentiles)	30	(12, 50)	81	(37, 112)	
Number of INR measurements per patient per month, median (10, 90 percentiles)	1.5	(0.87, 2.6)	3.8	(2.0, 5.0)	< 0.001
Time in therapeutic range, median (10, 90 percentiles), %	65.9	(34.7, 92.3)	78.1	(43.8, 92.5)	< 0.001
INR variance, median (10, 90 percentiles)	0.33	(0.16, 0.81)	0.22	(0.12, 0.56)	< 0.001
Extreme INR values, % (n)	5.3	(207)	1.8	(173)	< 0.001
INR values ≤ 1.5, % (n)	4.1	(160)	1.2	(120)	< 0.001
INR values ≥ 5.0, % (n)	1.2	(47)	0.54	(53)	0.077

Abbreviation: INR, international normalized ratio.
[a]Wilcoxon signed rank test.

(►**Table 2**). The patients' indications for warfarin therapy are given in ►**Table 2**. Sixty-two (49%) patients had used warfarin for 2 years before enrolment, all 126 patients passed the written test after 21 weeks of training in PSM and 77 (61%) patients completed 2 years with PSM (►**Supplementary Table S2**, available in the online version). The median frequency of INR testing per month was higher during PSM compared with conventional management (3.8 vs. 1.5 per month, $p < 0.001$; ►**Table 3**).

Time in Therapeutic Range

The median value of TTR increased from 65.9 to 78.1% during conventional management and PSM, respectively ($p < 0.001$; ►**Table 3**). The mean increase in TTR was 8.3% (95% confidence interval [CI]: 5.2–12, $p < 0.001$). There was no difference in TTR between training in self-management and PSM (2.3, 95% CI: –0.83, 5.4), and there was no difference between women and men (data not shown). In total, 50% ($n = 63$) of the patients had an increase in TTR $\geq$ 10% from the conventional management period to the PSM period, while 18% ($n = 23$) of the patients had a decrease in TTR $\geq$ 10% from the conventional management period to the PSM period. There was a 50% decrease and a 39% increase in the percentages of patients with TTR $< 40\%$ and $> 80\%$, respectively, from conventional management to PSM (►**Fig. 1**).

INR Variance, Extreme INR Values, and Complications

The median value of the INR variance decreased from 0.33 during conventional management to 0.22 during PSM ($p < 0.001$; ►**Table 3**). The percentage of extreme INR values (INR values ≤ 1.5 and ≥ 5.0) was lower during PSM compared with conventional management (5.3% vs. 1.8%, $p < 0.001$; ►**Table 3**). There was an increase in TTR after 0.5 years with PSM, thereafter a slight decrease and unchanged after 1 and 2 years (►**Fig. 2A**). INR variance was stable between training and 0.5 year with PSM, but increased after 1 year compared with training (►**Fig. 2B**). INR variance also increased after 1.5 and 2 years with PSM compared with training and 0.5 year with self-management (►**Fig. 2B**). A negative correlation between TTR and INR variance was found during conventional

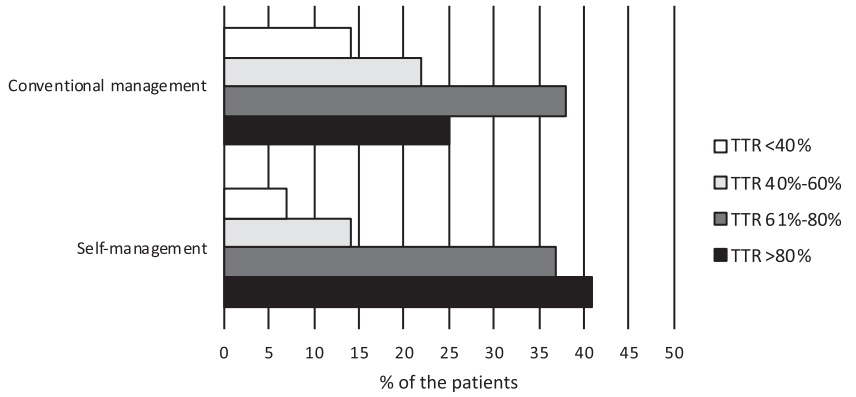

Fig. 1 Percentage of the patients with time in therapeutic range (TTR) $< 40\%$, 40–60%, 61–80%, and $> 80\%$ during conventional management and self-management.

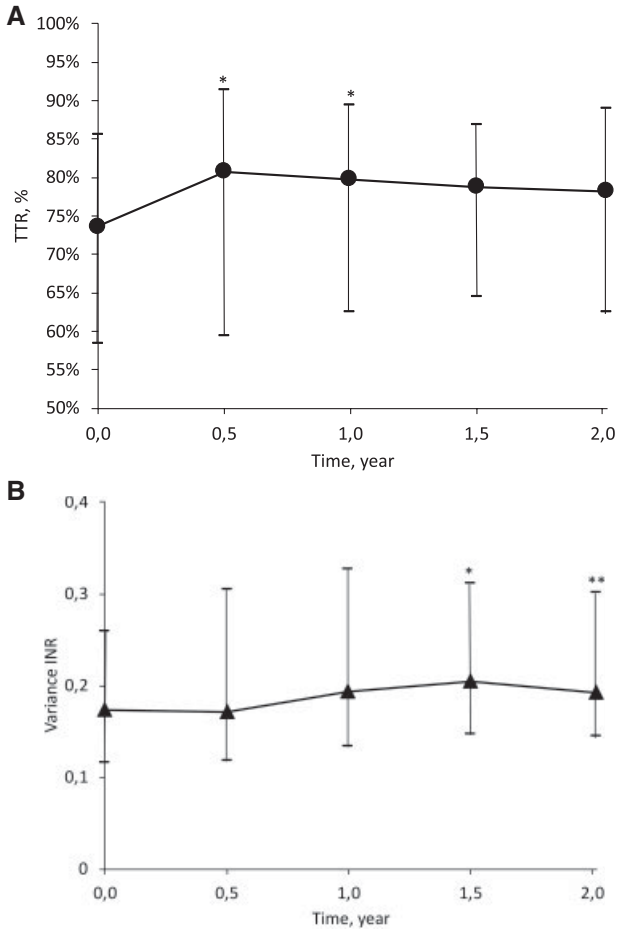

Fig. 2 Median with 25th–75th percentiles error bars for (**A**) time in therapeutic range (TTR) and (**B**) variance of international normalized ratio (INR) during training (0.0 year) and at different time points during self-management (0.5 year: $n = 123$ [97%], 1 year: $n = 116$ [91%], 1.5 years: $n = 108$ [85%], 2 years: $n = 77$ [61%]). $^{*}p < 0.05$ compared with training (0.0), $^{**}p < 0.05$ compared with training (0.0) and 0.5 year with self-management (Wilcoxon signed-rank test).

management and PSM (►**Supplementary Table S3**, available in the online version). For conventional management and PSM, a positive correlation was found between INR variance and the frequency of INR measurements (►**Supplementary Table S3**, available in the online version). For conventional management, a negative correlation between the frequency of INR measurements and TTR was found (►**Supplementary Table S4**, available in the online version). When excluding six patients with high frequency of INR measurements (between 4.2 and 5.4 INR measurements per month) and low TTR (between 33 and 57%) in the conventional management period (►**Supplementary Table S5**, available in the online version), there was no longer a significant correlation between frequency of INR measurements and TTR in the conventional management period. Thromboembolic events and major hemorrhage were reported for 2.4 ($n = 3$) and 3.2% ($n = 4$) of the patients, respectively, during the conventional management. No thromboembolic events or major hemorrhage were reported during PSM.

Quality of Life

QoL improved after 2 years with PSM compared with baseline (►**Table 4**). There was an increase in general management satisfaction and self-efficacy ($p < 0.001$; ►**Table 4**). Daily hassles, psychological distress, and a strained social network decreased after 2 years with PSM compared with baseline ($p < 0.001$; ►**Table 4**). There was no correlation between TTR and QoL at baseline or after 2 years with PSM (►**Supplementary Table S6**, available in the online version).

Discussion

In the present study, we found that the quality of warfarin therapy in Norway improved when the patients were transferred from conventional management to self-management. This is the first study that have used five different measures for the quality of VKA, and there was an increase in TTR, a

Table 4 Quality of life (QoL) before training in self-management (baseline) and after two years with self-management ($n = 103$)[a]

	General treatment satisfaction	Self-efficacy	Distress	Daily hassles	Strained social network
Baseline (before training)					
Median (10, 90 percentile)	3.4 (1.9, 5.2)	5.0 (3.8, 5.8)	3.0 (1.6, 4.5)	2.3 (1.3, 3.4)	2.0 (1.0, 3.9)
Cronbach's alpha	0.72	0.36	0.82	0.60	0.84
Self-management					
Median (10, 90 percentile)	5.8 (4.4, 6.0)	5.8 (4.8, 6.0)	2.3 (1.1, 3.7)	1.6 (1.0, 3.0)	1.4 (1.0, 2.6)
Cronbach's alpha	0.68	0.36	0.74	0.59	0.80
Difference self-management – baseline	2.00	0.57	–0.67[b]	–0.53[b]	–0.65[b]
p-Value[c]	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

Note: On a scale from 1 (doesn't apply) to 6 (applies fully). Internal reliability is indicated by Cronbach's alpha. For general treatment satisfaction and self-efficacy, improvement is indicated by an increase in scores. For distress, daily hassles, and strained social network, a decrease in the scores indicate improvement.

[a]Six patients did not answer the QoL questionnaire before training and 24 patients did not answer the QoL questionnaire after self-management. Two of these did not answer the QoL questionnaire either before or after.

[b]Negative values mean less distress, daily hassles, and strained social network.

[c]Wilcoxon signed-rank test.

decrease in INR variance, a decrease in extreme INR values and complications, and an improvement in all the five management-related QoL topics after 2 years with PSM of warfarin therapy compared with 2 years with conventional management.

TTR, INR variance, extreme INR values, and complications: Several studies have shown that the risk of complications increases with INR values outside the therapeutic range,[10,25,26] and the deviation/variability of the INR measurements correlates with the number of thromboembolic events, bleedings events, and mortality.[26,27] Thus, the two measures together provide more information about risk for adverse events than TTR alone[28] as TTR reflects the achievement of appropriate anticoagulation intensity regimen and INR variability measures stability of anticoagulation. TTR, INR variance, and extreme INR values are therefore often used as surrogate measures for the quality of VKA therapy. In the present study, fewer complications occurred during PSM compared with conventional management. However, due to the fact that only 126 patients participated in this study, complications cannot be used as a primary outcome.[10] Furthermore, the risk of thromboembolism and bleeding increase dramatically at INR below 1.5 and above 5.0, respectively.[29,30] Hence, the improvements in the surrogate measures during PSM of VKA therapy may potentially be extrapolated to a beneficial effect of this management strategy on clinical outcome.

Our results are in line with previous studies from other countries where TTR were similar[31–36] or higher[37–39] during PSM compared with conventional management. However, a direct comparison was difficult since the studies varies, for example, how patients were selected, number of patients, indications for VKA therapy, age, observation time, duration of the training, and quality of the conventional management. Thus, TTR during conventional management has been reported to vary from 47% in Germany[38] to 77% in the United Kingdom.[31] In the previous pilot study performed in Norway, there was no difference in TTR when the patients were transferred from conventional management to PSM (TTR 70% vs. 75%, respectively).[17] However, in that study there were only 23 patients, and the follow-up time was only 28 weeks.

The number of patients with TTR > 80% increased from 25% during conventional treatment to 41% during PSM (►**Fig. 1**), while a crossover study from the Netherlands found that only 27% of the patients had TTR > 75% during PSM versus 12% in the anticoagulation-clinic management period.[40] A 10% difference in TTR is defined as clinically significant,[41] and 50% of the patients in our study had an increase in TTR of 10% or more when changing from conventional management to PSM. Eighteen percent of the study population ($n = 23$) had a 10% or more decrease in TTR during PSM. This is in line with the study from the Netherlands reporting that 10 of 49 patients (20%) had better control of anticoagulation in the anticoagulation-clinic management than during PSM.[40] In our study, 13 of these 23 patients mainly had INRs above the therapeutic range, and 10 patients had INRs below the therapeutic range. It may be speculated that these patients probably are not suitable for self-management and should be transferred back to conventional management or be offered more support also after the training. To rapidly identify patients who experience worse control when self-managing, the patients are recommended to see their GP for a follow-up two to three times a year. In addition, they are instructed to send their INR values to their GP every 12th week and of course contact emergency department or their GP, depending upon symptoms, if they experience symptoms related to possible complications. In case of an extreme INR value (≥ 5.0) and when opening a new box with strips, they are instructed to contact their GP and perform a parallel INR analysis at the GP office or at the hospital. Patients with poor control have an individually closer follow-up by the GP, and some are transferred to only do self-measurement (i.e., they measure INR themselves, but the GP is contacted to do the warfarin dosing). To optimize the scheme, a continuous revision based on feedback from the patients is performed by Noklus. Furthermore, a plan for analytical quality control of the INR instruments is under elaboration.

The decrease in the percentages of extreme INR values from the conventional period to the PSM period (5.3% vs. 1.8%, $p < 0.001$; ►**Table 3**) in this study is in line with the previous pilot study from Norway (6.8% vs. 1.0%, $p < 0.001$).[17] However, this is in contrast to the study from the Netherlands where PSM was compared with anticoagulation-clinic-management, where no difference in extreme INR values was found (3.5% vs. 5.3%).[40]

We found a moderate negative correlation between TTR and INR variance (conventional management: –0.36, PSM: –0.42; ►**Supplementary Table S3**, available in the online version). These results are comparable with a previous cohort study from Sweden with approximately 20,000 patients with atrial fibrillation which also found a negative correlation (–0.27) between the TTR and standard deviation of transformed INR values.[27] Furthermore, our results are similar to a cohort study from the United States with approximately 40,000 patients aged > 65 years where the negative correlation between the TTR and log INR variability was –0.34.[28] However, while TTR was stable during 2 years with PSM, INR variance increased after 1.5 and 2 years with PSM compared with training and 0.5 years with PSM (►**Fig. 1**). It must be emphasized that the number of patients gradually decreased from 126 that completed the training in PSM to 77 (61%) that completed 2 years with PSM (►**Supplementary Table S2**, available in the online version). However, when we included only these 77 patients in the calculations, the same results for TTR were obtained while INR variance increased only after 2 years with PSM compared with training and 0.5 years with PSM (data not shown). Also, in a study from Germany an increase in INR deviation was seen between 6 and 12 months with PSM.[22] In contrast, in a randomized controlled trial from Austria with patients aged ≥ 60 years, TTR increased from 70.6 to 75.4% at 6 and 12 months, respectively, with no change in INR variance.[39] In that study, there was a follow-up visit every 6 months with PSM. Also, in a cohort study from Denmark, a decrease in event rates was observed from 1 year and after 5 years in 615 patients with mechanical heart valve performing PSM.[9] Nevertheless, our results could indicate that despite the ability

of patients to self-manage VKA therapy, some support may be considered also after the training. In Norway, the responsibility for the follow-up of the VKA therapy is transferred back to the GP after training, while in Denmark the patients are followed up by the anticoagulant clinic where the patients were trained for self-management.[42] Thus, a randomized controlled trial showed that anticoagulation clinics provided better VKA therapy than family physicians,[43] possibly because increased knowledge of VKA therapy seems to increase the quality of treatment.[44]

Time within therapeutic INR target range is dependent on the frequency of testing.[45] Furthermore, studies have shown that the variability in INR can be reduced by weekly INR measurements.[46] This may partly explain the increase in TTR and decrease in INR variance during PSM compared with conventional management as the number of measurements increased from 1.5 to 3.8 per month (►**Table 3**). However, in studies where the frequency of INR testing was similar during PSM and conventional management the quality of VKA therapy was comparable (INR testing about every 9 days)[40] or better (a smaller variance of INR; INR testing about once a month)[46] during PSM. In addition, in trials comparing PSM and patients who received training without performing self-monitoring there were no difference in the quality in VKA therapy.[36,47] Thus, increased knowledge contributes to improved compliance and individualization which are factors that have shown to improve the quality of anticoagulation.[48] Hence, it appears that the improvement is provided by the total concept of PSM with training over time, increased knowledge, increase in the frequency of testing, and focus. We cannot tell which of these factors are of most importance. Furthermore, PSM offers the opportunity to measure INR more often, while this is often not achievable in a busy GP practice.

Quality of Life

The improvement in QoL after 2 years with PSM confirms the earlier pilot study from Norway[16] and is in line with previous studies using the same questionnaire in other countries like the Netherlands,[40] Germany,[49] and Canada[36] where the follow-up time was shorter (from 28 weeks to 6 months). QoL was not correlated with TTR at baseline or after 2 years with PSM. This probably reflects that many aspects of QoL are not affected by the quality of anticoagulant treatment.

Number of Participants

Between 10 and 80% of patients using warfarin are estimated to be suitable for PSM.[8,13] The patients in this study were recruited from approximately 220 GP offices, an outpatient clinic at a hospital in addition to advertisement in a local newspaper and at a Web page. GPs in Tromsø and Bodø have in total approximately 1,200 to 1,500 patients each. However, we do not have data on how many eligible patients each GP office had or how many patients were asked to participate. Thus, our recruitment technique does not allow to calculate a "response rate" of invited participants. Still, since approximately 1% of the population in Norway use warfarin, the total number of patients using warfarin available for recruitment in this study was approximately 1,200 to 2,000. Thus, the 132 patients recruited in this study constitute approximately 10% of this population.

Strengths and Limitations

This is the first study that have used five outcome measures (TTR, INR variance, extreme INR values, complications, and QoL) for quality VKA therapy, and they were all in favor of PSM. In addition, the observation period was longer for both the conventional and PSM phase compared with previous studies[31,32,34–36,39,46] were the follow-up varied from 26 weeks[32] to 12 months.[34,39] Furthermore, the number of patients was also higher compared with most of the earlier studies.[22,31,33,35–40,46] We do not have complete data for all patients for 4 years. However, there were 62 patients during 2 years with conventional treatment and 77 patients during 2 years with PSM, which is more than most of the previous studies.[31,33,35–37,40,46] A "limitation" of our design could be the lack of randomization and blinding. However, blinding is not possible in this kind of study. The use of this design, however, was a substantial strength of the trial as it was able to control for differences between groups because the subjects acted as their own control. The exclusion of patients over 70 years of age may limit the generalizability of the findings, but we assume that also patients older than 70 years who have the required physical and mental health, are motivated and have the expected level of compliance with PSM will be able to perform PSM. However, older patients need more training time than younger patients.[50] The training program with a duration of 21 weeks may seem quite extensive compared with some of the previous studies.[22,32,34,37,39,40] However, the total duration (number of hours) with lectures is comparable with other studies. In our set-up, the patients gradually become self-managed, and the accuracy of the POC INR instrument is monitored by comparison with a laboratory instrument. About 1,200 patients have been trained in self-management by Noklus using the same training program, demonstrating that this training program also is feasible in a clinical setting. The training program has been adapted from the program they offer at Aarhus University Hospital in Denmark where more than 1,500 patients have been trained. Due to the limited number of training sessions, the trainers (physicians and BLS or nurses) probably do not use more time on this program compared with a shorter program with about the same content.

Conclusion

In conclusion, we found that the quality of warfarin therapy improved when patients were transferred from conventional management of warfarin therapy to PSM. This is the first study using four different measures for the quality of VKA. There was an increase in TTR, a decrease in INR variance, a decrease in extreme INR values, and complications. In addition, there was an improvement in all the five management-related QoL topics after 2 years with PSM of warfarin therapy compared with baseline. To further improve the quality of

VKA therapy, there should be an increased use of PSM for eligible patients.

What is known about this topic?

- Several studies show that patient self-management (PSM) of oral anticoagulant therapy with vitamin K antagonists (VKAs) reduces the risk of complications compared with conventional management.
- Studies have also shown that time in therapeutic range (TTR) during PSM is equal to or higher than during conventional management with improved quality of life (QoL).
- There is limited knowledge about the quality of self-management of warfarin therapy in Norway.

What does this paper add?

- This is the first study using five different outcome measures (TTR, INR variance, extreme INR values, complications, and QoL) for the quality of PSM of warfarin therapy. An improvement was found in all measures after 2 years when transferred from conventional management in Norway.
- The improvement is probably provided by the total concept of PSM with training over time, increased knowledge, and focus, as well as the increased frequency of INR testing.
- To further improve the quality of VKA therapy, there should be an increased use of PSM for eligible patients.

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Conflict of interest
A.H.K. reports grants from The Western Regional Health Authorities, during the conduct of the study. All the other authors report no conflict of interest.

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