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Complete List of Authors:	Talboom-Kamp, Esther; LUMC, Public Health and Primary Care Department; SALTRO Diagnostic Centre, Verdijk, Noortje; LUMC, Public Health and Primary Care Department; SALTRO Diagnostic Centre, Kasteleyn, Marise; LUMC, Public Health and Primary Care Department Harmans, Lara; SALTRO Diagnostic Centre, Talboom, Irvin; Zorgdraad Foundation Numans, Mattijs; LUMC, Public Health and Primary Care Department Chavannes, Niels; LUMC, Public Health and Primary Care Department
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Equivalent health status for e-learning, group training self-management or usual care in oral anticoagulation patients: a parallel cohort design in the PORTALS Study

EPWA Talboom-Kamp MD MBA[1 2], NA Verdijk MSc PhD[1 2], MJ Kasteleyn MSc PhD[1], LM Harmans MSc[2], IJSH Talboom[3], ME Numans MD PhD[1], NH Chavannes MD PhD[1]

[1] Leiden University Medical Centre, Public Health and Primary Care Department
P.O. Box 9600, 2300 RC Leiden, the Netherlands

[2] Saltro Diagnostic Centre
Mississippidreef 83, 3565 CE Utrecht, the Netherlands

[3] Zorgdraad Foundation
Wijnand van Arnhemweg 54, 6862XN Oosterbeek, the Netherlands

Corresponding author

EPWA (Esther) Talboom-Kamp MD MBA
Saltro Diagnostic Centre
Mississippidreef 83
3565 CE Utrecht
The Netherlands
Telephone: +31-30-2361170
Fax: +31-30-2361172
E-mail: e.talboom@saltro.nl

PORTALS study

Abstract

Objectives To analyze the effect on health status and self-management skills of the implementation of self-management programs, including eHealth by e-learning versus group training.

Setting A primary Care Thrombosis Service Center.

Participants Of the 247 OAT patients, 63 started a self-management program by e-learning, 74 self-management by group training, and 110 received usual care.

Intervention and methods Parallel cohort design with two randomized self-management groups (e-learning and group training) and a third group receiving usual care. Multilevel linear regression modeling was used to analyze the effect of implementation of self-management on time in therapeutic range (TTR). Linear regression analysis was used to analyze usage of a supporting eHealth platform and the impact on self-efficacy (Generalized Self-Efficacy Scale; GSES) and education level. After intervention, TTR was measured in 3 time periods of 6 months each.

Main outcome measures These were i) health status (TTR, severe complications), ii) usage of an eHealth platform, and iii) determinants (GSES, education level).

Results Analysis of the three groups showed no significant differences in TTR between the three time periods (p=0.520), between the groups (p=0.460) or between the groups over time (p=0.263). Comparison of e-learning and group training showed no significant differences in TTR between the time periods (p=0.614), between the groups (p=0.460) or between the groups over time (p=0.263). No association was found between GSES and TTR (p=0.717), or between education level and TTR (p=0.107). No significant difference was found between the two self-management groups in usage of the platform in the three time periods (0-6 months p=0.571; 6-12 months p=0.866; 12-18 months p=0.260).

Conclusions No differences were found between OAT patients trained by e-learning or by a group course regarding health status, TTR, and usage of a supporting eHealth platform. The TTR was similar in both the self-management and regular care patients.

Trial Registration – NTR3947

PORTALS study

Keywords – oral anticoagulation; TTR; eHealth; self-management; self-efficacy; e-learning; thrombosis; self-monitoring.

Article summary

Strengths and limitations of this study

- This study provides practical insight into successful implementation of self-management programs consisting of high-quality training and usage of a patient platform;
- The study findings add important evidence to the existing body of knowledge on implementation of eHealth;
- The needed number of participants was not entirely met in one of the groups;
- Behavioral changes require time, whereas the study period was restricted to 18 months;
- Patients were free to volunteer, which might have caused bias in our study groups.

Introduction

Venous thromboembolism (VTE) and atrial fibrillation (AF) are common causes of mortality and morbidity, with rising prevalence and medical costs [1] [2] [3]. Oral anticoagulation therapy (OAT) reduces thromboembolic events in AF, prosthetic heart valves, acute myocardial infarction and other conditions, and is an effective treatment for VTE [4] [5] [6]. The major risks of OAT are bleeding complications, with a rate of major bleeding among long-term users of vitamin K antagonists (VKAs) of 1.5-5.2% per year [7] [8] [9]. There is a narrow therapeutic range for OAT, expressed as the international normalized ratio (INR); INR values ≥ 4.5 increase the risk of major bleeding and values ≥ 2 increase the risk of thromboembolism [10] [11]. This is relevant, as patients have considerable difficulty in maintaining adequate adherence to VKA regimens, with a significant effect on anticoagulation control [12]. Structured monitoring and coaching of patients using VKA is essential. This may be carried out by specialized centers in primary care or in hospitals [13]. Alternatively, patients might choose to self-manage their VKA monitoring. In the case of OAT, self-management includes monitoring INR values by patients (self-monitoring) and, as a possible next step, self-adjustment of the medication dosage (self-dosage). Nowadays, patients using self-management programs are usually supported by tailor-made eHealth platforms, because eHealth interventions have proven effective in stimulating self-management [14]. Self-management provides more freedom for the patient, improves quality of life and self-efficacy, and lightens the burden of specialized centers [15] [16]. Research shows a reduction of thromboembolic events and a reduction in all-cause mortality for patients with self-management [17]. These improvements are due to the fact that patients have greater responsibility in their disease management together with increased awareness, commitment and interest in their condition [18].

Recently other anticoagulants, novel or non-vitamin K antagonist oral anticoagulants (NOACs), have been introduced and are increasingly preferred as an alternative for VKA as they do not require frequent monitoring [19]. However, data on the effects of NOAC use in routine clinical practice are still lacking, although disadvantages and risks have been reported. Monitoring of kidney function is necessary, and compliance with medication intake is also very important for NOACs [20] [21]. Thus, adequate self-management is important for all patients with OAT, irrespective of the type of medicine they use. Adequate self-management requires individual ability to deal with self-monitoring, symptoms, treatment, and the physical and social consequences of a disease. The basic principle of self-management is that behavioral change cannot succeed without patients accepting their own responsibility; this behavioral change is necessary to improve the quality of life of patients and the primary outcomes of their health and disease [22]. Research on chronic diseases such as PORTALS study

diabetes [23], COPD [24], and heart failure [25] has shown that aspects such as self-efficacy (belief in one's capabilities to organize and execute the course of action required to produce given attainments), educational level, socioeconomic status (SES), age and sex are influencing factors in successful self-management and predictors in eHealth usage [26].

As education is the basic approach in the development of self-management skills, the strategy used to implement educational support is expected to affect the individual level of self-management and, thereby, clinical outcomes. To test this hypothesis, we designed the PORTALS study. The aim of this study was to analyze the effect of the implementation of a self-management program, including eHealth by e-learning versus a group training. In addition, we aimed to investigate the relationship between the implementation strategy, health status, self-management skills and individual patient characteristics. In the design of the PORTALS study, both self-monitoring and self-dosage of medication are considered important self-management skills.

Methods

Study design

For the PORTALS study, we designed a quality improvement intervention and compared strategies in an implementation study [27]. Two methods were developed to train long-term OAT patients of the Saltro Thrombosis Service (outpatient anticoagulation clinic and laboratory) in self-management routine care. Using this design, we aimed to examine the influence of the training strategy on clinical outcomes and usage of the supporting eHealth platform. Full methodological details are reported elsewhere [28]; Figure 1 presents an overview of the study design.

A parallel cohort design was used to investigate determinants of optimal implementation of self-management by comparing two different training methods. After inclusion, participants were randomly divided into subgroups: one group was trained and educated by e-learning (group 1) and the other group received face-to-face group training (group 2). Patients unable or unwilling to dose their medication were free to continue with only self-monitoring. Patients who did not wish to start with self-management were invited to participate in the non-self-management group, i.e. a parallel cohort group receiving usual care (group 3). Group 3 provided valuable information about the patients who were unable/unwilling to use an online supported self-management program.

Based on our parallel cohort design, comparison between e-learning and group training for self-management (group 1 and 2) and non-self-management patients (group 3) is applicable, considering the specific conditions in the choice of the statistics.

Participants

The present study focused on patients of the Saltro Thrombosis Service who voluntarily chose to start with self-management. The inclusion criteria for patients to start with self-management were a long-term indication for anticoagulants, internet access, and stable INR values (at least three INR values in succession must be within therapeutic range). Patients who met the criteria for self-management were approached for participation in the study. Because self-management (including eHealth) is already a regular care process of the Saltro Thrombosis Service, the group training was also open to patients who were not willing to participate in the study. The e-learning was reserved for participants of the present study, as this was a new implementation method. All patients provided written informed consent before participation in the study.

Patient involvement

Patients were neither involved in the design, nor in defining research questions and outcome measures of the study; however, they were actively involved in the development of the self-management platform Portavita. To maximize the involvement of patients we did not randomize the intervention groups (self-management and usual care); we chose a recruitment design in which patients of the Thrombosis Service voluntarily chose to start with self-management. During the study patients could give feedback on the intervention and on the self-management platform; their satisfaction was continuously monitored. Feedback from patients made it possible to optimize their care. All patients will be informed about the results of this study.

Recruitment of patients and non-participation

Patients of the Saltro Thrombosis Service who received regular care were eligible for recruitment. In 2013, 8950 patients received usual care from the Saltro Thrombosis Service of which 85% had a long-term indication. From June 2013 onward, a random selection of 1632 patients was approached for participation in the present study using three methods, i) information and invitation by letter, ii) personal invitation by specialized nurses, and iii) invitation by telephone. Patients who did not wish to start with self-management were invited to participate in a parallel cohort group receiving usual care (group 3), thereby providing valuable information about non-participants. Baseline

characteristics of all regular patients of the Saltro Thrombosis Service also provided valuable information about non-participants.

Intervention

The intervention in group 1 and 2 consisted of a training program in combination with the use of an online self-management platform called Portavita. In group 1, patients used an e-learning that was specifically designed for the PORTALS study (Multimedia Appendix 1).

Table 1 summarizes the e-learning modules in group 1, the group training modules in group 2, and the basic training in group 3.

Table 1. Training methods in group 1, 2 and 3.

Group 1	Group 2	Group 3
• General education (e-learning) about anticoagulation + test • Selftesting device • Training (e-learning) selftesting + use of web portal • Three months of e-learning + selftesting	• Group course with training selftesting + use of web portal • Three weeks practice at home • Group course about anti coagulation • Three months of training at home	• Basic training
• Selftesting device	• Selftesting device	• Venipuncture at home or in facilities
• Control and quality check by nurse • Continuing self-management program + Control and quality check by nurse every six months	• Control and quality check by nurse • Continuing self-management program + Control and quality check by nurse every six months	• Written instructions by Thrombosis doctor

In the PORTALS study, the online self-management portal used is called Portavita (Multimedia Appendix 2). This application combines a patient portal and a healthcare provider portal. The healthcare portal leaves space for the OAT protocol, medication records, and information about complications. The Portavita Anticoagulation Self-management patient portal has become widely accepted; it provides patients with a diary tool for self-monitoring and self-dosage, education, it also allows personal notes, and healthcare professionals can send advice and notes to the patient. It implies that the patient analyzes a drop of blood using a home INR monitor. The patient can access the web-based patient portal to enter the INR and specific information for the health professional (intervention, bleeding, change in medication, vacation, etc.). Clinically validated inbuilt algorithms

provide advice regarding the next dose and test interval. The only things needed are an internet connection and a device like a PC, tablet or smartphone. When logging on (username + password) for the first time to Portavita, every user was directed to the homepage. From there, users could access all functionalities of the portal. The logon procedure of this portal is based on Dutch security legislation and guidelines (the Dutch Personal Data Protection Act).

Data collection

INR values, thromboembolic events, bleedings, medication and indication were monitored and registered continuously by patients in the portal and by professionals of the Saltro Thrombosis Service. We measured the INR, complications and medication during a period of 6 months before and 18 months after starting the intervention (i.e. 24 months in total). The data collection also consisted of questionnaires (at baseline, and after each 3 x 6-month period) to measure the determinants and outcomes. Patients of group 1 and 2 received these questionnaires by e-mail, and patients in group 3 by e-mail or by post. In addition, the number of self-tests and use of the portal were continuously registered in the portal. Data on the total population of the Saltro Thrombosis Service were also collected.

Outcome measures and determinants

The primary outcome of this study was health status expressed as the INR control over time and severe complications (bleedings and thromboembolic events). To summarize the INR control over time, the percentage of time in therapeutic range (TTR) of INR was used, calculated with the Rosendaal method [29]. TTR values were calculated for two INR ranges (INR 2-3 and INR 2-3.5) because different calculations are used in Dutch and in international guidelines. TTR was measured at four moments: at 6 months before intervention, and at 3 x 6-month periods (total of 18 months) after starting the intervention. Serious complications were defined as those needing treatment or medical evaluation. An independent thrombosis specialist was responsible for classifying serious complications at the end of the trial. The total follow-up period for all these measures was 24 months.

Furthermore, the self-management skills of participants were evaluated. Self-management skills were defined as usage of the self-management platform, reflected as the amount of login sessions. Self-monitoring and self-dosage are registered within the same login session. The usage counts were analyzed. The determinants were self-efficacy and socio-demographic characteristics. Self-efficacy was measured at baseline using the Generalized Self-Efficacy Scale (GSES), with items scored on a

four-point scale with a higher score reflecting higher self-efficacy [30]. Socio-demographic characteristics were assessed by an online questionnaire addressing the following characteristics: age, gender, education level, marital status, working status (labor), and quality of life (QoL), which was assessed using the EuroQol-5D (EQ-5D) and displayed at baseline. The EQ-5D is a 5-item questionnaire with a higher score reflecting a higher QoL.

Sample size and statistical methods

To detect a relevant effect of the new implementation strategy of e-learning or group training (>5%) [31] at a power 80% and α=0.05, we calculated that a sample size of 63 patients was required per group. Considering a 15% drop out, 72 (63/0.85) patients were needed per study group. Baseline characteristics between the three groups were explored using Chi-square tests and Kruskal-Wallis tests.

To investigate the effect of the different implementation methods of training versus the parallel cohort group on TTR and complications, multilevel linear regression modeling (mixed models) was used. First, outcomes were compared between the three groups. A second (mixed models) analysis was used to compare the difference in effect between e-learning and group training (group 1 vs. group 2) on TTR and complications. Analyses were adjusted for age and gender.

To examine the impact of GSES and education on the effect of the different implementation methods, multiple linear regression analyses were performed with TTR at time point 3 as outcome, and GSES and education as predictors. Analyses were adjusted for age and gender.
A linear regression analysis was used to analyze usage (mean number of login sessions) of the portal Portavita in group 1 and 2.

Results

A total of 1632 OAT patients of the Saltro Thrombosis Service was approached to participate in the study. A randomly selected group of 475 patients was informed by letter; of these, 233 responded and 59 were willing to participate. Then, 692 patients were personally invited by specialized nurses after thorough information about self-management; of these, 139 patients were interested to participate in the study. In addition, 234 were also interested in self-management but did not want to participate in the study. Trained research assistants approached 465 patients by telephone with information about the possibility of self-management and the study; of these, 111 were willing to

participate. In addition, 52 patients signed up for self-management but were not willing to participate in the study. During the process of inviting patients for the PORTALS study, patients were asked about their reasons for not participating: the main reasons were not having a computer or internet, no digital skills, the effort of participating in a trial, and their high level of satisfaction with usual care.

Participants were included in the study only after providing written informed consent but, because some patients failed to do this, 247 participants were finally included. Of these, 110 continued to receive regular care (group 3) and 137 patients were randomly divided into group 1 and 2 using a computer program. After randomization, 63 patients were included in group 1 (e-learning) and 74 in group 2 (group training). Figure 2 summarizes the recruitment process, including the reasons for loss to follow-up.

Characteristics of the total population of the Thrombosis Service

The characteristics of all OAT patients of the Saltro Thrombosis Service in 2015 are shown in Table 2.

Table 2. Clinical characteristics of the population of the Saltro Thrombosis Service.

Total patients N	11132
Male N (%)	6009 (54.0)
Self-management N (%)	1986 (17.8)
Male self-management N (%)	1260 (63.4)
Medication	
Acenocoumarol N (%)	8360 (75.1)
Phenprocoumon N (%)	2761 (24.8)
Warfarin N (%)	11 (0.1)
Indications	
AF N (%)	7430 (66.8)
Ven thromboembolism N (%)	1673 (15.0)
Artificial valve N (%)	720 (6.5)
Other N (%)	1309 (11.8)
Severe complications	
Major bleedings N (%)	219 (2.0)
Thromboembolism N (%)	85 (0.8)

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Baseline characteristics of study participants

Table 3 presents the baseline characteristics of the participants: median age was 66.9 years, and median TTR was 54.7 (for INR range 2-3) and 79.1 (for INR range 2-3.5). Of these patients, 66% had an indication of AF and 77.3% used acenocoumarol as oral anticoagulation medication. No significant differences were found between the three groups for gender, TTR, indication, and marital status. Group 3 differed significantly from group 1 and 2 on age, baseline GSES and EQ-5D, use of medication, education level, and work status (Table 3).

Table 3. Baseline characteristics of patients with Oral Anticoagulation Therapy in the PORTALS study

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	Group 1	Group 2	Group 3	p-value	Total
N	63	74	110		247
Age in years* [IQR]	65.0[a] [56.2-67.7]	65.8[a] [56.4-70.4]	69.6[b] [64.0-74.9]	0.00**	66.9 [59.5-72.7]
Males N (%)	47 (74.6)	52 (70.3)	81 (73.6)	0.826	180 (72.9)
TTR INR range 2-3 (%)* [IQR]	50.2 [39.1-67.1]	52.9 [39.0-68.6]	57.4 [40.1-75.1]	0.159	54.7 [39.8-70.7]
TTR INR range 2-3.5 (%)* [IQR]	76.3 [67.0-86.0]	77.1 [64.1-85.3]	85.6 [72.0-93.5]	0.159	79.1 [68.2-88.8]
GSES* [IQR]	3.5[a] [3.1-3.8]	3.3[a,b] [3.0-3.7]	3.1[b] [2.9-3.5]	0.001**	3.3 [3.0-3.7]
EQ5D* [IQR]	1.0[a] [0.81-1.0]	0.84[a,b] [0.78-1.0]	0.84[b] [0.78-1.0]	0.036**	0.84 [0.81-1.0]
Indication AF N (%) Ven thromboembolism N (%) Artificial valve N (%) Other N (%)	 42 (66.7) 13 (20.6) 2 (3.2) 6 (9.5)	 44 (59.5) 18 (24.3) 3 (4.1) 9 (12.2)	 77 (70.0) 11 (10.0) 4 (3.6) 18 (16.4)	0.215	 163 (66) 42 (17) 9 (3.6) 33 (13.4)
Medication Acenocoumarol N (%) Phenprocoumon N (%) Warfarin N (%)	 51 (81)[a] 10 (15.9)[a] 2 (3.2)[a]	 64 (86.5)[a] 10 (13.5)[a] 0 (0)[a]	 76 (69.1)[b] 34 (30.9)[b] 0 (0)[a]	0.004**	 191 (77.3) 54 (21.9) 2 (0.8)
Education level Low N (%) Medium N (%) High N (%)	 7 (12.1)[a] 24 (41.4)[a] 27 (46.6)[a]	 13 (19.1)[a] 32 (47.1)[a] 23 (33.8)[b]	 33 (35.9)[b] 46 (50.0)[a] 13 (14.1)[c]	0.00**	 53 (24.3) 102 (46.8) 63 (28.9)
Marital status Married N (%) Widow N (%) Divorced N (%) Single N (%)	 49 (84.5) 1 (1.7) 1 (1.7) 7 (12.1)	 50 (73.5) 6 (8.8) 6 (8.8) 6 (8.8)	 73 (79.3) 4 (4.3) 4 (4.3) 11 (12.0)	0.280	 172 (78.9) 11 (5.0) 11 (5.0) 24 (11.0)
Labour No paid work N (%) Paid work N (%) Household N (%) Incapacitated N (%)	 28 (48.3)[a] 19 (32.8)[a] 8 (13.8)[a] 3 (5.2)[a]	 29 (42.6)[a] 20 (29.4)[a] 11 (16.2)[a] 8 (11.8)[a]	 39 (42.4)[a] 14 (15.2)[b] 23 (25.0)[a] 16 (17.4)[a]	0.043**	 96 (44.0) 53 (24.3) 42 (19.3) 27 (12.4)

***Values are medians and corresponding Interquartile Ranges [IQR]**
**** Between-group differences (P < 0.05) are indicated by ****
Each superscript (a,b,c) letter denotes a subset of sample categories which do not differ significantly from each other at the 0.05 level.
TTR is the therapeutic international normalized ratio (INR) range, GSES is the General Self-efficacy Scale, EQ5D EuroQol five dimensions questionnaire is a standardized instrument for use as a measure of health outcome.
N Missing questionnaires: GSES 29, EQ5D 32, indication 0, medication 0, education 29, marital status 29, labour 29.

Health status before and after intervention

Figure 3A shows the TTR values using the INR 2-3 in the three groups, 6 months before the intervention and in the 3 x 6-month periods after the intervention; the TTR values using the INR 2-3.5 are presented in Figure 3B (Appendix 3).

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Analysis of the three groups showed no significant difference in TTR values over time (p=0.520), between the groups (p=0.398), or between the groups over time (p=0.418).

Analysis of the two self-management groups showed no significant differences in TTR values between the four time periods (p=0.614). Also, no significant differences in TTR were found between group 1 and 2 (p=0.460) or between these two groups over time (p=0.263).

The sensitivity analyses showed that using an INR of 2-3.5, instead of 2-3, had no marked effect on the results, although a significant time effect was found. Results are presented in figure 3B in Appendix 3.

During the 18-month period after the intervention, across all three groups, a total of 3 severe complications occurred (3/247=1.2%): i.e. two muscular bleedings in the e-learning group (2/63=3.2%) and one cerebrovascular accident among patients receiving group training (1/74=1.4%); no complications occurred in the usual care group.

Educational level and GSES

Educational level was not associated with the TTR in the last 6 months (p=0.107); education level did not modify the effect of the different implementation methods on TTR (p=0.161).
No association was found between the GSES and TTR in the last 6 months (p=0.717); GSES did not modify the effect of the different implementations methods on TTR (p=0.174).

Usage of the platform

Figure 4 presents the usage by patients in group 1 and 2 (using the logfiles of the Portavita platform) during the 18 months after start of the intervention. Patients logged on to the platform to register their INR; some also used it to establish their medication dosage or to communicate with healthcare professionals of the Thrombosis Service. There was no significant difference between group 1 and 2 in usage of the platform during the three time periods (0-6 months p=0.571; 6-12 months p=0.866; 12-18 months p=0.260).

Discussion

In the present study, no differences were found in health status and usage of the platform between anticoagulation self-management patients trained by e-learning and by group training. Moreover, PORTALS study

the clinical results for self-management patients were similar to those of patients receiving regular care. Therefore, we conclude that, with adequate training through e-learning or group training, self-management is safe and reliable for a selected proportion of motivated patients receiving OAT. The PORTALS study provides valuable information on different implementation methods of OAT self-management, including eHealth.

Strengths and limitations

This PORTALS study has several strengths. First, the study investigates the effect of different education programs in a situation as close to 'real life' as possible, integrated in a self-management program including eHealth, on clinical outcomes and self-management skills. The study also adds evidence to the existing body of knowledge on implementation of eHealth; this is important because local political/financial factors have a major impact on successful integration of eHealth in daily practice and because self-management is important for patients who will use VKAs and NOACs in the future [32].

This study also has limitations. First, a randomized controlled trial (RCT) was not feasible in our setting of an implementation design in a real-life healthcare system with patients who have differing demands. Instead, an observational study was considered the best option for our context, i.e. patients cannot be denied or forced to start with self-management. Furthermore, self-management skills imply behavioral changes. However, behavioral changes require time, whereas the study period was restricted to 18 months. This study also has limitations typically associated with eHealth trials. For example, as patients were free to volunteer, bias might have occurred in our study groups. Users were self-selected and were, presumably, motivated to use the education program (including the web-based platform) as would be expected in a real-life setting. Of the 1632 invited OAT patients, 247 patients (15%) were willing to participate and provided informed consent. However, only 137 patients (8.4% of invited patients) wanted to participate in the self-management groups and were randomized; other studies have a similar low recruitment rate for self-management trials [33]. This phenomenon might have affected the measurability of differences and might also reduce differences between the groups.

The total population of the Thrombosis Service showed a lower percentage of men than the participants of the present study, although the distribution of indications/medication was similar. In the total population, the percentage of severe complications was low (bleedings 2%,

thromboembolism 0.8%); during our study period the percentage of complications was also low (group 1=1.4%; group 2=1.2%; group 3=0%), indicating a high quality of thrombosis care.

During the process of inviting patients for the PORTALS study, we asked their reasons for not participating (main reasons were: not having a computer/internet, no digital skills, the effort of participating, and their high level of satisfaction with usual care). The group with usual care differed significantly from the self-management groups on several baseline characteristics: i.e. patients in usual care were older, had a lower education level, and fewer of them had paid work. Also, they had a lower GSES and EQ5D, and made less use of acenocoumarol. Patients in the total population of the Thrombosis Service, and in the usual care group, might have different wishes and expectations towards care than patients that chose for a self-management program; i.e. self-management programs are suitable for patients that are highly motivated and have skills for self-management tasks.

Finally, to measure a significant difference in health status, 72 patients were needed in each group. Although these numbers were not entirely met in group 1 (e-learning), analysis of the groups should be sufficiently powered to detect relevant differences. In addition, the high number of INR data points collected before and after the intervention has a substantial impact on the strength of the design and the multilevel linear analysis.

Due to these limitations, caution is required when generalizing our results to general practice. However, the practical applicability of our results for other specialized OAT centers is positive, i.e. the study provides practical insight into successful implementation of self-management programs consisting of high-quality training and usage of a patient platform.

Interpretation of findings

No overall significant differences in health status were found between the three groups. Therapeutic INR control was good in all groups; in the last 6 months of the intervention period, all groups spent around 58% of time within the narrow therapeutic range 2-3 and 83% of time within the therapeutic range 2-3.5; this indicates high quality and is comparable to other studies [33] [34]. It is reported that any management model should demonstrate anticoagulation control levels around 60% for TTR of INR range 2-3 to be considered safe [34] [35] [36]. In studies conducted outside specialized care facilities in several different regions, INR readings ranged from 40-70% of the time within target range using an existing care delivery system [13]. In the present study, the quality of OAT

management can be considered high in all groups. Since the routine OAT management is already of high quality, further improvement of TTR is difficult to achieve. Furthermore, the national guidelines for the INR range changed during the last 6 months of our PORTALS study; this had a negative impact on the TTR during our last measurement period. Complication rates also compared favorably with international data; our overall adverse event rate was low compared to other studies, including studies on NOACs [37] [38] [39].

Self-efficacy and educational level of users had no impact on health status for the different implementation methods. The construct of perceived self-efficacy reflects an optimistic self-belief [30]; a correlation can be understood based on the belief that one can perform a novel or difficult task, or cope with adversity (indicating a higher self-efficacy). In the present study, self-efficacy was comparable to that in a healthy Dutch population [40] [41].

Usage of the Portavita portal remained high during the 18-month study period and attrition was low. Usually, the 'law of attrition' (the phenomenon of participants stopping usage) is a common finding in eHealth evaluations and an important challenge in the evaluation of eHealth applications [42]. The practical value of the Portavita portal is very high for patients, because of the functionalities of self-monitoring, self-dosage and digital advice from professional healthcare providers. Because patients use the self-management program, regular visits to medical facilities are unnecessary. Patients can manage their anticoagulation in their own time and in their own chosen place. Thus, using the self-management program gives them (extra) freedom; this might be a strong motivating factor for using the program. Also, the training programs were sound and sustainable during the entire study period, probably stimulating patients to persevere with their self-management program. Moreover, e-learning and group training led to the same usage and, therefore, the same self-management skills. Therefore, we conclude that our e-learning and group training provide a good start for OAT patients that voluntarily start with a self-management program including eHealth.

Self-management programs with eHealth technologies for chronic conditions can be used to enhance self-management and revise the Chronic Care Model; patients who actively participate in their care achieve valuable and sustained improvement in wellbeing [43] [44]. In many eHealth studies, use of a Personal Health Record or self-management platform can promote an informed/activated patient and augment the Chronic Care Model for self-management support and productive interactions; even though a direct dosage-effect relation (usually analyzed in a classical RCT) is not common in eHealth [45]. Self-management programs with good training and practical eHealth platforms have

the potential to make chronic care personalized in a blended care model; every patient needs a different approach for an optimal health status. Healthcare providers need to embrace a different role and release tight protocols [46]. Individual patients have different expectations and wishes, which should be a topic of conversation with each patient.

More studies are needed (preferably with larger sample groups, and including non-users) to gain more insight into the preferences of various patient groups, as well as the related costs.
The substantial workload generated by integrating a web-based platform in an OAT self-management program emphasizes the importance of piloting and assessing workforce implications for OAT management centers. The present results provide additional insight into the organizational aspects of the implementation of education programs into a self-management program with a platform, including the need to educate and coach patients in the use of web-based platforms.

Conclusion

Our main finding is that there were no differences in health status and usage of a supporting eHealth platform between anticoagulation self-management patients trained by e-learning and by group training. Moreover, we found that clinical results for self-management patients are comparable to those of patients receiving usual care. We conclude that with appropriate and sound training through e-learning or group training, self-management is safe and reliable for a selected proportion of motivated patients receiving oral anticoagulation treatment. The PORTALS study provides valuable information on different implementation methods of oral anticoagulation self-management, including eHealth.

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Data sharing

Data will be made available for sharing where available and appropriate.

PORTALS study

Transparency declaration

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.
All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Ethics and consent to participate

This study is conducted according to the principles of the Declaration of Helsinki (version 59, 2008) and in accordance with the Medical Research Involving Human Subjects Act (WMO). Participants were only included in the study after written informed consent was received. The Medical Ethics Committee of the LUMC approved this study (Reference No. P12.278).

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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Author's contributions

ET is the principle investigator and contributed to all aspects of the research. NV assisted on all aspects. MK assisted on the statistical analysis and is responsible for revising the manuscript several times. LH is responsible for revising the manuscript several times. IT is responsible for the acquisition of data and revising the manuscript several times. MN is responsible for revising the manuscript. NC is responsible for the concept, design, and for revising the manuscript. All authors read and approved the final manuscript.

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	Saltro Thrombosis Service Centre		
	Self-Management		Usual Care
Patients	Group 1	Group 2	Group 3
	#72	#72	#72
Instruction	E-Learning • disease-specific knowledge • self-testing skills • use of the web-portal • (voluntary) self-adjustment of medication	Group Course • disease-specific knowledge • self-testing skills • use of the web-portal • (voluntary) self-adjustment of medication	Basic Short Training
Platform	Self-management	Self-management	-

Figure 1. Overview of the study design: details of groups 1, 2 and 3

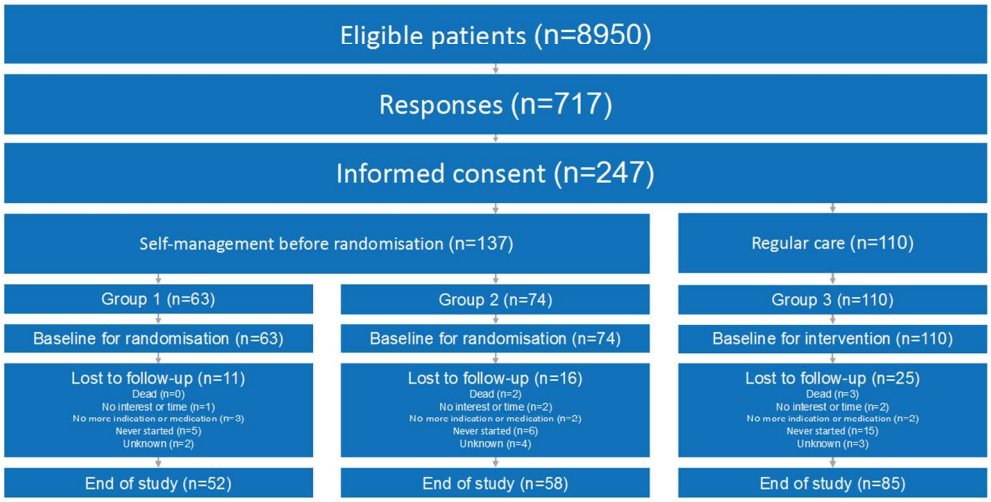


Figure 2. Flowchart of the PORTALS study.

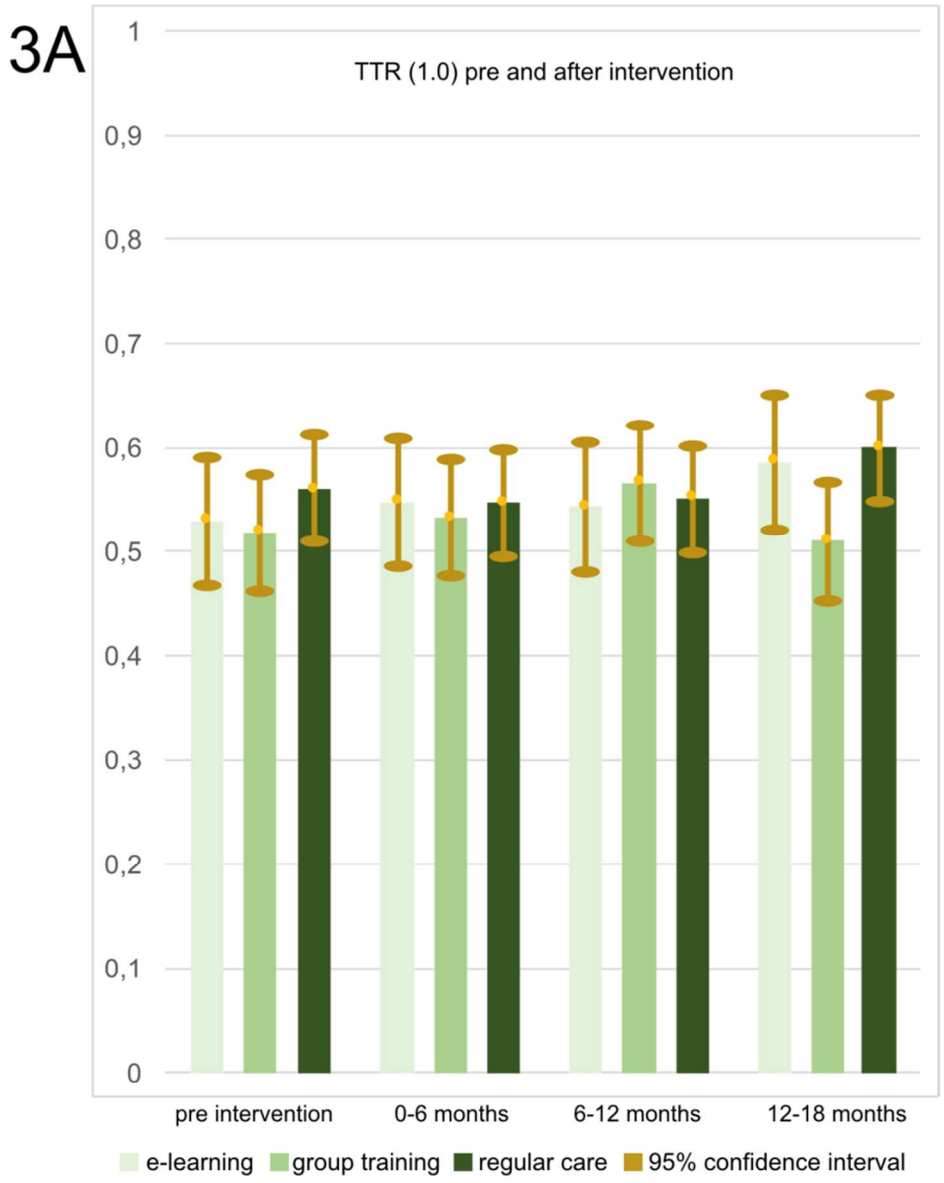


Figure 3A. Health status based on time in therapeutic (TTR) (for INR range 2-3) for the three groups.

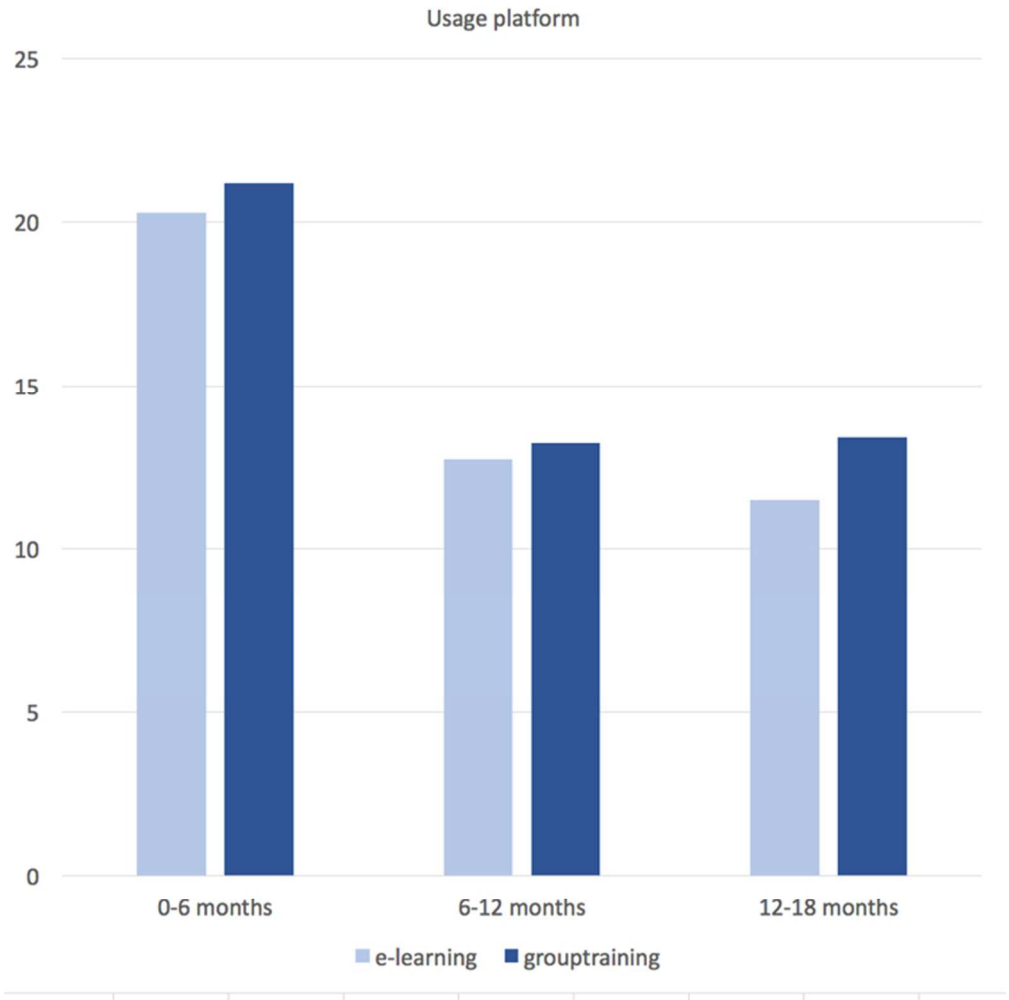
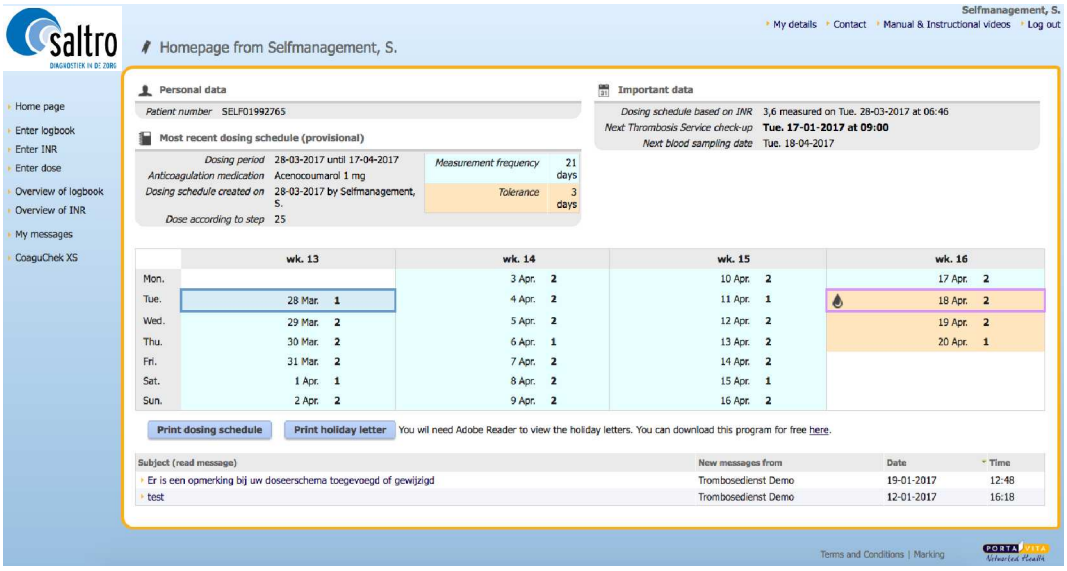
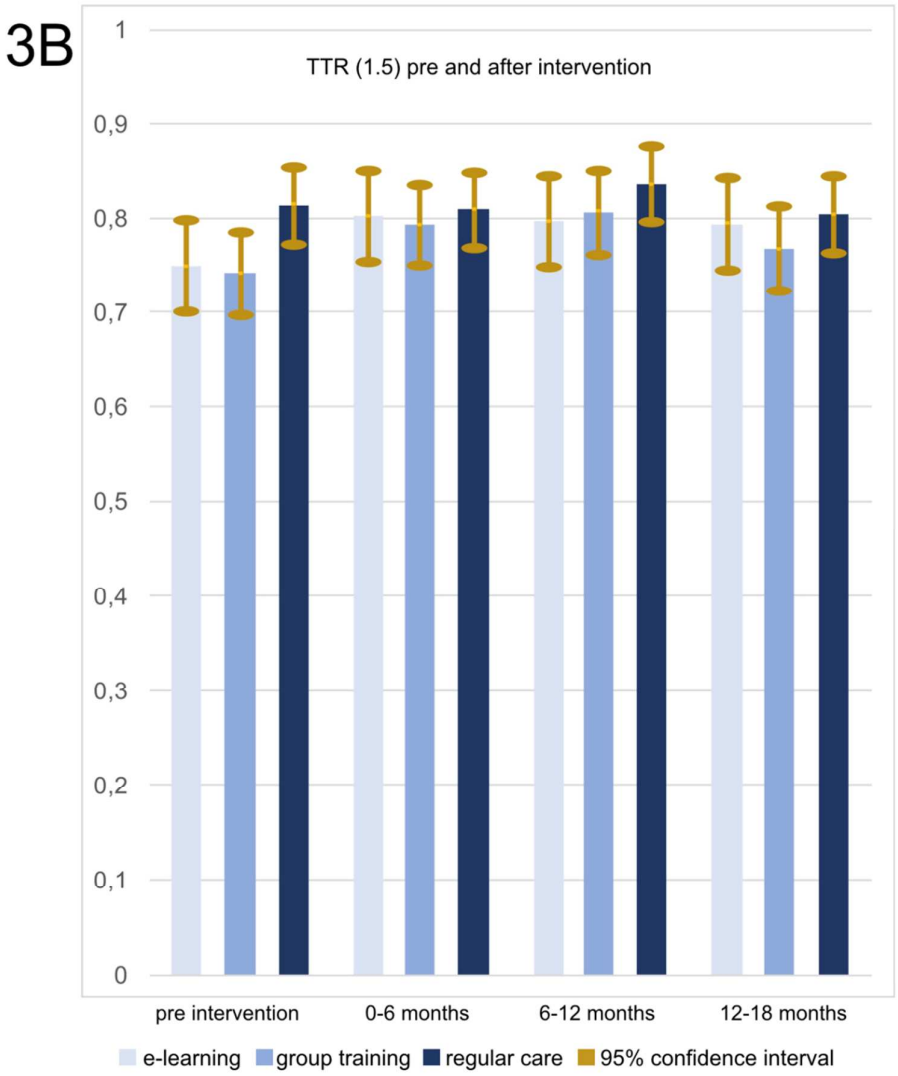


Figure 4. Usage of participants in group 1 and group 2 after start of the intervention.

Appendix 1: E-learning anticoagulation



Appendix 2: Patients' self-management web portal homepage



Appendix 3: Health status based on time in therapeutic (TTR) (for INR range 2-3.5) for the three groups. Figure 3B shows TTR values using the INR 2-3.5 in the three groups, 6 months before the intervention and in the 3 x 6-month periods after the intervention. Analysis of the three groups showed that the TTR values differed significantly over time (p=0.017). No significant differences were found in TTR between the groups (p=0.163) or between the groups over time (p=0.545).

Analysis of the two self-management groups showed significant differences in the TTR values between the four time periods (i.e. pre- and postintervention) (p=0.008). There were no significant differences in TTR between group 1 and 2 (p=0.721) or between the groups over time (p=0.825).

Equivalent health status for e-learning, group training self-management or usual care in oral anticoagulation patients: a parallel cohort design in the PORTALS Study

STROBE statement, checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract		
	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract – Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found – Page 2
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported – Page 3 (Introduction)
Objectives	3	State specific objectives, including any prespecified hypotheses – Page 4 (Introduction)
Methods		
Study design	4	Present key elements of study design early in the paper – Page 5/6 (Study design) + figure 1
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection – Page 5 (Study design) + reference 28
Participants	6	(*a*) *Cohort study*?Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up – Page 6 (Participants) + reference 28
		(*b*) *Cohort study*?For matched studies, give matching criteria and number of exposed and unexposed Participants were not matched + figure 1
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give

	Item No	Recommendation
		diagnostic criteria, if applicable – Page 8/9 (Outcome measures and determinants)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). – Page 8/9 (Outcome measures and determinants) Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias – Page 9 (Sample size and statistical methods)
Study size	10	Explain how the study size was arrived at – Page 9 (Sample size and statistical methods)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why – Page 8/9 (Outcome measures and determinants)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding – Page 9 (Sample size and statistical methods)
		(*b*) Describe any methods used to examine subgroups and interactions – Page 9 (Sample size and statistical methods)
		(*c*) Explain how missing data were addressed – Page 9 (Sample size and statistical methods)
		(*d*) *Cohort study*?If applicable, explain how loss to follow-up was addressed – Page 9 (Sample size and statistical methods)
		(*e*) Describe any sensitivity analyses Not applicable.
Results		
Participants	13*	(*a*) Report numbers of individuals at each stage of study?eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed – Page 9/10 (Results)
		(*b*) Give reasons for non-participation at each stage – Page 10/11 (Baseline characteristics of study participants)
		(*c*) Consider use of a flow diagram Figure 2.
Descriptive data	14*	(*a*)Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders – Page 10/11 (Baseline characteristics of study participants)

	Item No	Recommendation
		(*b*) Indicate number of participants with missing data for each variable of interest – Page 10/11 (Baseline characteristics of study participants) + Table 3
		(*c*) *Cohort study*?Summarise follow-up time (eg average and total amount) – Page 8/9 (Outcome measures and determinants)
Outcome data	15*	*Cohort study*?Report numbers of outcome events or summary measures over time – Page 12/13 (Usage of the platform)
Main results	16	(*a*) Report the numbers of individuals at each stage of the study?eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed – Page 9/10 (Results)
		(*b*) Give reasons for non-participation at each stage – Page 9/10 (Results)
		(*c*) Consider use of a flow diagram Figure 2.
Other analyses	17	Report other analyses done?eg analyses of subgroups and interactions, and sensitivity analyses Page 12 (Health status before and after intervention/Educational level and GSES)
Discussion		
Key results	18	Summarise key results with reference to study objectives – Page 13 (Discussion)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias – Page 13/14 (Strenghts and limitations)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence – Page 14/15 (Interpretation of findings)
Generalisability	21	Discuss the generalisability (external validity) of the study results – Page 16 (Interpretation of findings)
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based – Page 17 (Funding)

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross sectional studies.

The STROBE checklist is best used in conjunction with the explanation and elaboration article.[18-20] This article and separate versions of the checklist for cohort, case-control, and cross sectional studies are available at www.strobe-statement.org.

BMJ Open

Equivalent therapeutic control for oral anticoagulation patients with e-learning, group training self-management or usual care: a parallel cohort design in Dutch primary care

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Primary Subject Heading:	Health services research
Secondary Subject Heading:	Health informatics, Medical education and training, General practice / Family practice
Keywords:	self-efficacy, eHealth, TTR, self-management, thrombosis, oral anticoagulation

Equivalent therapeutic control for oral anticoagulation patients with e-learning, group training self-management or usual care: a parallel cohort design in Dutch primary care

EPWA Talboom-Kamp MD MBA[1 2], NA Verdijk MSc PhD[1 2], MJ Kasteleyn MSc PhD[1], LM Harmans MSc[2], IJSH Talboom[3], ME Numans MD PhD[1], NH Chavannes MD PhD[1]

[1] Leiden University Medical Centre, Public Health and Primary Care Department
P.O. Box 9600, 2300 RC Leiden, the Netherlands

[2] Saltro Diagnostic Centre
Mississippidreef 83, 3565 CE Utrecht, the Netherlands

[3] Zorgdraad Foundation
Wijnand van Arnhemweg 54, 6862XN Oosterbeek, the Netherlands

Corresponding author

EPWA (Esther) Talboom-Kamp MD MBA
Saltro Diagnostic Centre
Mississippidreef 83
3565 CE Utrecht
The Netherlands
Telephone: +31-30-2361170
Fax: +31-30-2361172
E-mail: e.talboom@saltro.nl

Abstract

Objectives To analyze the effect on therapeutic control and self-management skills of the implementation of self-management programs, including eHealth by e-learning versus group training.

Setting Primary Care Thrombosis Service Center.

Participants Of the 247 OAT patients, 63 started self-management by e-learning, 74 self-management by group training, and 110 received usual care.

Intervention and methods Parallel cohort design with two randomized self-management groups (e-learning and group training) and a group receiving usual care. The effect of implementation of self-management on time in therapeutic range (TTR) was analyzed with multilevel linear regression modeling. Usage of a supporting eHealth platform and the impact on self-efficacy (Generalized Self-Efficacy Scale; GSES) and education level were analyzed with linear regression analysis. After intervention, TTR was measured in 3 time periods of 6 months.

Main outcome measures i) TTR, severe complications ii) usage of an eHealth platform iii) GSES, education level.

Results Analysis showed no significant differences in TTR between the three time periods (p=0.520), the three groups (p=0.460) or the groups over time (p=0.263). Comparison of e-learning and group training showed no significant differences in TTR between the time periods (p=0.614), the groups (p=0.460) or the groups over time (p=0.263). No association was found between GSES and TTR (p=0.717), or education level and TTR (p=0.107). No significant difference was found between the self-management groups in usage of the platform (0-6 months p=0.571; 6-12 months p=0.866; 12-18 months p=0.260). The percentage of complications was low in all groups (3.2%; 1.4%; 0%).

Conclusions No differences were found between OAT patients trained by e-learning or by a group course regarding therapeutic control (TTR) and usage of a supporting eHealth platform. The TTR was similar in self-management and regular care patients. With adequate e-learning or group training, self-management is safe and reliable for a selected proportion of motivated VKA patients.

Trial Registration – NTR3947

Keywords – oral anticoagulation; TTR; eHealth; self-management; self-efficacy; e-learning; thrombosis; self-monitoring.

Article summary

Strengths and limitations of this study

- This study provides practical insight into successful implementation of self-management programs consisting of high-quality training and usage of a patient platform;
- The study findings add important evidence to the existing body of knowledge on implementation of eHealth;
- The needed number of participants was not entirely met in one of the groups;
- Behavioral changes require time, whereas the study period was restricted to 18 months;
- Patients were free to volunteer, which might have caused bias in our study groups.

Introduction

Venous thromboembolism (VTE) and atrial fibrillation (AF) are common causes of mortality and morbidity, with rising prevalence and medical costs [1] [2] [3]. Oral anticoagulation therapy (OAT) reduces thromboembolic events in AF, prosthetic heart valves, acute myocardial infarction and other conditions, and is an effective treatment for VTE [4] [5] [6]. The major risks of OAT are bleeding complications, with a rate of major bleeding among long-term users of vitamin K antagonists (VKAs) of 1.5-5.2% per year [7] [8] [9]. There is a narrow therapeutic range for VKA, expressed as the international normalized ratio (INR) with an optimal intensity, related to a low rate of events, between 2.5 and 4.9 [10] [11]. This is relevant, as patients have considerable difficulty in maintaining adequate adherence to VKA regimens, with a significant effect on anticoagulation control [12]. Structured monitoring and coaching of patients using VKA is essential. This may be carried out by specialized centers in primary care or in hospitals [13]. Alternatively, patients might choose to self-manage their VKA monitoring. In the case of VKA, self-management includes monitoring INR values by patients (self-monitoring) and, as a possible next step, self-adjustment of the medication dosage (self-dosage). Nowadays, patients are usually supported by improved eHealth supported self-management programs [14] with more freedom, improved quality of life and self-efficacy, and less burden of specialized centers [15] [16]. Research shows a reduction of thromboembolic events and in all-cause mortality for patients with self-management [17], due to the fact that patients have greater responsibility, increased awareness, commitment and interest in their condition [18].

Adequate self-management is important for all patients with OAT to improve adherence to medication, irrespective of the type of anticoagulation medicine they use [19] [20] [21]. The basic principle of self-management is behavioral change, which is necessary to improve the quality of life of patients and the primary outcomes of their health and disease [22]. Research on chronic diseases such as diabetes [23], COPD [24], and heart failure [25] has shown that aspects such as self-efficacy (belief in one's capabilities to organize and execute the course of action required to produce given attainments), educational level, socioeconomic status (SES), age and sex are influencing factors in successful self-management and predictors in eHealth usage [26].

As education is the basic approach in the development of self-management skills, the strategy used to implement educational support is expected to affect the individual level of self-management and, thereby, clinical outcomes. To test this hypothesis, we designed the PORTALS study. The aim of this study was to analyze the effect on anticoagulation control of an intervention consisting of an education program in combination with the use of an online self-management portal. The general

definition of self-management is the individual's ability to manage the symptoms, treatment, physical and psychosocial consequences and life style changes inherent in living with a chronic condition [27]; in line with this definition, both self-monitoring and self-dosage of medication are considered important self-management skills in the PORTALS study.

Methods

Study design

For the PORTALS study, we designed a quality improvement intervention and compared strategies in an implementation study [28]. Two methods were developed to train long-term VKA patients of the Saltro Thrombosis Service (outpatient anticoagulation clinic and laboratory) in self-management routine care. Using this design, we aimed to examine the influence of the training strategy on clinical outcomes and usage of the supporting eHealth platform. Full methodological details are reported elsewhere [29]; Table 1 presents an overview of the study design.

Table 1. Overview of the study design: details of groups 1, 2 and 3

	Saltro Thrombosis Service Centre		
	Self-Management		Usual Care
Patients	Group 1	Group 2	Group 3
	#72	#72	#72
Instruction	**E-Learning** Disease-specific knowledge Self-testing skills Use of the web-portal (voluntary) Self-adjustment of medication	**Group Course** Disease-specific knowledge Self-testing skills Use of the web-portal (voluntary) Self-adjustment of medication	**Basic Short Training**
Platform	Self-management	Self-management	

A parallel cohort design was used to investigate determinants of optimal implementation of self-management by comparing two different training methods. After inclusion, participants were randomly divided into subgroups: one group was trained and educated by e-learning (group 1) and the other group received face-to-face group training (group 2). Patients unable or unwilling to dose

their medication were free to continue with only self-monitoring. Patients who did not wish to start with self-management were invited to participate in the non-self-management group, i.e. a parallel cohort group receiving usual care (group 3). Group 3 provided valuable information about the patients who were unable/unwilling to use an online supported self-management program.

Based on our parallel cohort design, comparison between e-learning and group training for self-management (group 1 and 2) and non-self-management patients (group 3) is applicable, considering the specific conditions in the choice of the statistics.

Participants

The present study focused on patients of the Saltro Thrombosis Service who voluntarily chose to start with self-management. The inclusion criteria for patients to start with self-management were a long-term indication for anticoagulants, internet access, and stable INR values (at least three INR values in succession must be within therapeutic range). Patients who met the criteria for self-management were approached for participation in the study. Because self-management (including eHealth) is already an option for patients of the Saltro Thrombosis Service, the group training was also open to patients who were not willing to participate in the study. The e-learning was reserved for participants of the present study, as this was a new implementation method. All patients provided written informed consent before participation in the study.

Patient involvement

Patients were neither involved in the design, nor in defining research questions and outcome measures of the study; however, they were actively involved in the development of the self-management platform Portavita. To maximize the involvement of patients we did not randomize the intervention groups (self-management and usual care); we chose a recruitment design in which patients of the Thrombosis Service voluntarily chose to start with self-management. During the study patients could give feedback on the intervention and on the self-management platform; their satisfaction was continuously monitored. Feedback from patients made it possible to optimize their care. All patients will be informed about the results of this study.

Recruitment of patients and non-participation

Patients of the Saltro Thrombosis Service who received regular care without a self-management program were eligible for recruitment. In 2013, 8950 patients received usual care from the Saltro Thrombosis Service of which 85% had a long-term indication. From June 2013 onward, a random

selection of 1632 patients was approached for participation in the present study using three methods, i) information and invitation by letter, ii) personal invitation by specialized nurses, and iii) invitation by telephone. Patients who did not wish to start with self-management were invited to participate in a parallel cohort group receiving usual care (group 3), thereby providing valuable information about non-participants. Baseline characteristics of all regular patients of the Saltro Thrombosis Service also provided valuable information about non-participants.

Intervention

The intervention in group 1 and 2 consisted of a training program in combination with the use of an online self-management portal called Portavita. In group 1, patients used an e-learning that was specifically designed for the PORTALS study (Multimedia Appendix 1).

Table 2 summarizes the programs in all groups: the e-learning modules in group 1, the group training modules in group 2, and the basic training in group 3. In group 1 the training was provided by e-learning that started with a personal login procedure and an online instruction; the interim control and quality checks were carried out by specialized nurses of the Thrombosis Service. The group course in group 2 was carried out by specialized and expert healthcare professionals. Both training methods had the same content, but were offered in a completely different manner.

Table 2. Training methods in group 1, 2 and 3.

Group 1	Group 2	Group 3
General education (e-learning) about anticoagulation + test Selftesting device Training (e-learning) selftesting + use of web portal Three months of e-learning + selftesting	Group course with training selftesting + use of web portal Three weeks practice at home Group course about anti coagulation Three months of training at home	Basic training
Selftesting device	Selftesting device	Venipuncture at home or in facilities

Control and quality check by nurse Continuing self-management program + Control and quality check by nurse every six months	Control and quality check by nurse Continuing self-management program + Control and quality check by nurse every six months	Written instructions by thrombosis doctor

In the PORTALS study, the online self-management portal used is called Portavita (Multimedia Appendix 2). This application combines a patient portal and a healthcare provider portal. The healthcare portal leaves space for the OAT protocol, medication records, and information about complications. The Portavita Anticoagulation Self-management patient portal has become widely accepted; it provides patients with a diary tool for self-monitoring and self-dosage, education, it also allows personal notes, and healthcare professionals can send advice and notes to the patient. It implies that the patient analyzes a drop of blood using a home INR monitor. The patient can access the web-based patient portal to enter the INR and specific information for the health professional (intervention, bleeding, change in medication, vacation, etc.). Clinically validated inbuilt algorithms provide advice regarding the next dose and test interval. The only things needed are an internet connection and a device like a PC, tablet or smartphone. When logging on (username + password) for the first time to Portavita, every user was directed to the homepage. From there, users could access all functionalities of the portal. The logon procedure of this portal is based on Dutch security legislation and guidelines (the Dutch Personal Data Protection Act).

Data collection

INR values, thromboembolic events, bleedings, medication and indication were monitored and registered continuously by patients in the portal and by professionals of the Saltro Thrombosis Service. We measured the INR, complications and medication during a period of 6 months before and 18 months after starting the intervention (i.e. 24 months in total). The data collection also consisted of questionnaires (at baseline, and after each 3 x 6-month period) to measure the determinants and outcomes. Patients of group 1 and 2 received these questionnaires by e-mail, and patients in group 3 by e-mail or by post. In addition, the number of self-tests and use of the portal were continuously registered in the portal. Data on the total population of the Saltro Thrombosis Service were also collected.

Outcome measures and determinants

The primary outcome of this study was therapeutic control expressed as the INR control over time and severe complications (bleedings and thromboembolic events). To summarize the INR control over time, the percentage of time in therapeutic range (TTR) of INR was used, calculated with the Rosendaal method [30]. TTR values were calculated for two INR ranges (INR 2-3 and INR 2-3.5) because different calculations are used in Dutch and in international guidelines. TTR was measured at four moments: at 6 months before intervention, and at 3 x 6-month periods (total of 18 months) after starting the intervention. Serious complications were defined as those needing treatment or medical evaluation. An independent thrombosis specialist was responsible for classifying serious complications at the end of the trial. The total follow-up period for all these measures was 24 months.

Furthermore, the self-management skills of participants were evaluated. Self-management skills were defined as usage of the self-management platform, reflected as the amount of login sessions. Self-monitoring and self-dosage are registered within the same login session. The usage counts were analyzed. The determinants were self-efficacy and socio-demographic characteristics. Self-efficacy was measured at baseline using the Generalized Self-Efficacy Scale (GSES), with items scored on a four-point scale with a higher score reflecting higher self-efficacy [31]. Socio-demographic characteristics were assessed by an online questionnaire addressing the following characteristics: age, gender, education level, marital status, working status (labor), and quality of life (QoL), which was assessed using the EuroQol-5D (EQ-5D) and displayed at baseline. The EQ-5D is a 5-item questionnaire with a higher score reflecting a higher QoL.

Sample size and statistical methods

To detect a relevant effect of the new implementation strategy of e-learning or group training (>5%) [32] at a power 80% and α=0.05, we calculated that a sample size of 63 patients was required per group. Considering a 15% drop out, 72 (63/0.85) patients were needed per study group. Baseline characteristics between the three groups were explored using Chi-square tests and Kruskal-Wallis tests.

To investigate the effect of the different implementation methods of training versus the parallel cohort group on TTR, multilevel linear regression modeling (mixed models) was used. First, TTR outcomes were compared between the three groups. A second (mixed models) analysis was used to compare the difference in effect between e-learning and group training (group 1 vs. group 2) on TTR.

The variable TTR was included as outcome in the model. The periods of TTR measurements (time), the group and the interaction term (time*group) were included as predictors.
Both analyses were adjusted for age and gender.

To examine the impact of GSES and education on the effect of the different implementation methods, multiple linear regression analyses were performed with TTR at time point 3 as outcome, and GSES and education as predictors. Analyses were adjusted for age and gender.
A linear regression analysis was used to analyze usage (mean number of login sessions) of the portal Portavita in group 1 and 2.

Results

A total of 1632 VKA patients of the Saltro Thrombosis Service were invited to participate, of which 56% (n=915) declined (Figure 1). Patients were invited in three different ways: by letter (n=475), by personal invitation during a visit to the Thrombosis Service (n=692) and by telephone (n=465). 717 patients were interested in participation in the study; 247 patients eventually signed an informed consent. During the process of inviting patients for the PORTALS study, patients were asked about their reasons for not participating: the main reasons were not having a computer or internet, no digital skills, the effort of participating in a trial, and their high level of satisfaction with usual care.

Participants were included in the study only after providing written informed consent but, because some patients failed to do this, 247 participants were finally included. Of these, 110 continued to receive regular care (group 3) and 137 patients were randomly divided into group 1 and 2 using a computer program. After randomization, 63 patients were included in group 1 (e-learning) and 74 in group 2 (group training). Figure 1 summarizes the recruitment process, including the reasons for loss to follow-up.

Characteristics of the total population of the Thrombosis Service

The characteristics of all VKA patients of the Saltro Thrombosis Service in 2015 are shown in Table 3.

Table 3. Clinical characteristics of the population of the Saltro Thrombosis Service.

Total patients N	11132

Male N (%)	6009 (54.0)
Self-management N (%)	1986 (17.8)
Male self-management N (%)	1260 (63.4)
Medication	
Acenocoumarol N (%)	8360 (75.1)
Phenprocoumon N (%)	2761 (24.8)
Warfarin N (%)	11 (0.1)
Indications	
AF N (%)	7430 (66.8)
Ven thromboembolism N (%)	1673 (15.0)
Artificial valve N (%)	720 (6.5)
Other N (%)	1309 (11.8)
Severe complications	
Major bleedings N (%)	219 (2.0)
Thromboembolism N (%)	85 (0.8)

Baseline characteristics of study participants

Table 4 presents the baseline characteristics of the participants: median age was 66.9 years, and median TTR was 54.7 (for INR range 2-3) and 79.1 (for INR range 2-3.5). Of these patients, 66% had an indication of AF and 77.3% used acenocoumarol as oral anticoagulation medication. No significant differences were found between the three groups for gender (χ^2_2=0.38, p=826), TTR (χ^2_2=3.68, p=0.159), indication (χ^2_2=8.33, p=0.215), and marital status (χ^2_2=7.47, p=0.280). The three groups differed significantly on age (χ^2_2=19.96, p=0.0), baseline GSES (χ^2_2=15.08, p=0.001) and EQ-5D (χ^2_2=6.66 , p=0.036), use of medication (χ^2_2=15.23 , p=0.004), education level (χ^2_2=23.72 , p=0.00), and work status (χ^2_2=13.01 , p=0.043) (Table 4).

Table 4. Baseline characteristics of patients with VKA therapy in the PORTALS study

	Group 1	Group 2	Group 3	p-value	Total
N	63	74	110		247
Age in years* [IQR]	65.0[a] [56.2-67.7]	65.8[a] [56.4-70.4]	69.6[b] [64.0-74.9]	0.00**	66.9 [59.5-72.7]
Males N (%)	47 (74.6)	52 (70.3)	81 (73.6)	0.826	180 (72.9)
TTR INR range 2-3 (%)* [IQR]	50.2 [39.1-67.1]	52.9 [39.0-68.6]	57.4 [40.1-75.1]	0.159	54.7 [39.8-70.7]
TTR INR range 2-3.5 (%)* [IQR]	76.3 [67.0-86.0]	77.1 [64.1-85.3]	85.6 [72.0-93.5]	0.159	79.1 [68.2-88.8]

GSES* [IQR]	3.5[a] [3.1-3.8]	3.3[a,b] [3.0-3.7]	3.1[b] [2.9-3.5]	0.001**	3.3 [3.0-3.7]
EQ5D* [IQR]	1.0[a] [0.81-1.0]	0.84[a,b] [0.78-1.0]	0.84[b] [0.78-1.0]	0.036**	0.84 [0.81-1.0]
Indication					
AF N (%)	42 (66.7)	44 (59.5)	77 (70.0)	0.215	163 (66)
Ven thromboembolism N (%)	13 (20.6)	18 (24.3)	11 (10.0)		42 (17)
Artificial valve N (%)	2 (3.2)	3 (4.1)	4 (3.6)		9 (3.6)
Other N (%)	6 (9.5)	9 (12.2)	18 (16.4)		33 (13.4)
Medication					
Acenocoumarol N (%)	51 (81)[a]	64 (86.5)[a]	76 (69.1)[b]	0.004**	191 (77.3)
Phenprocoumon N (%)	10 (15.9)[a]	10 (13.5)[a]	34 (30.9)[b]		54 (21.9)
Warfarin N (%)	2 (3.2)[a]	0 (0)[a]	0 (0)[a]		2 (0.8)
Education level					
Low N (%)	7 (12.1)[a]	13 (19.1)[a]	33 (35.9)[b]	0.00**	53 (24.3)
Medium N (%)	24 (41.4)[a]	32 (47.1)[a]	46 (50.0)[a]		102 (46.8)
High N (%)	27 (46.6)[a]	23 (33.8)[b]	13 (14.1)[c]		63 (28.9)
Marital status					
Married N (%)	49 (84.5)	50 (73.5)	73 (79.3)	0.280	172 (78.9)
Widow N (%)	1 (1.7)	6 (8.8)	4 (4.3)		11 (5.0)
Divorced N (%)	1 (1.7)	6 (8.8)	4 (4.3)		11 (5.0)
Single N (%)	7 (12.1)	6 (8.8)	11 (12.0)		24 (11.0)
Labour					
No paid work N (%)	28 (48.3)[a]	29 (42.6)[a]	39 (42.4)[a]	0.043**	96 (44.0)
Paid work N (%)	19 (32.8)[a]	20 (29.4)[a]	14 (15.2)[b]		53 (24.3)
Household N (%)	8 (13.8)[a]	11 (16.2)[a]	23 (25.0)[a]		42 (19.3)
Incapacitated N (%)	3 (5.2)[a]	8 (11.8)[a]	16 (17.4)[a]		27 (12.4)

***Values are medians and corresponding Interquartile Ranges [IQR]**

**** Between-group differences (P < 0.05) are indicated by ****

Each superscript (a,b,c) letter denotes a subset of sample categories which do not differ significantly from each other at the 0.05 level.

TTR is the therapeutic international normalized ratio (INR) range, GSES is the General Self-efficacy Scale, EQ5D EuroQol five dimensions questionnaire is a standardized instrument for use as a measure of health outcome.

N Missing questionnaires: GSES 29, EQ5D 32, indication 0, medication 0, education 29, marital status 29, labour 29.

Therapeutic control before and after intervention

Figure 2A shows the TTR values using the INR 2-3 in the three groups, 6 months before the intervention and in the 3 x 6-month periods after the intervention; the TTR values using the INR 2-3.5 are presented in Figure 2B (Appendix 3).

Analysis of the three groups showed no significant difference in TTR values over time ($F_{3,631}$=0.755, p=0.520), between the groups ($F_{2,211}$=0.924, p=0.398), or between the groups over time ($F_{6,631}$=1.009, p=0.418).

Analysis of the two self-management groups showed no significant differences in TTR values between the four time periods ($F_{3,378}$ =0.602, p=0.614). Also, no significant differences in TTR were found between group 1 and 2 ($F_{3,378}$ =0.548, p=0.460) or between these two groups over time ($F_{3,378}$ =1.335, p=0.263).

The sensitivity analyses showed that using an INR of 2-3.5, instead of 2-3, had no marked effect on the results, although a significant time effect was found. Results are presented in figure 2B in Appendix 3.

During the 18-month period after the intervention, across all three groups, a total of 3 severe complications occurred (3/247=1.2%): i.e. two muscular bleedings in the e-learning group (2/63=3.2%) and one cerebrovascular accident among patients receiving group training (1/74=1.4%); no complications occurred in the usual care group.

Educational level and GSES

Educational level was not associated with the TTR in the last 6 months ($F_{2,198}$=2.263, p=0.107); education level did not modify the effect of the different implementation methods on TTR ($F_{4,198}$=1.659, p=0.161).

No association was found between the GSES and TTR in the last 6 months ($F_{1,198}$=0.132, p=0.717); GSES did not modify the effect of the different implementations methods on TTR ($F_{2,198}$=1.762, p=0.174).

Usage of the platform

Figure 3 presents the usage by patients in group 1 and 2 (using the logfiles of the Portavita platform) during the 18 months after start of the intervention. Patients logged on to the platform to register

their INR; some also used it to establish their medication dosage or to communicate with healthcare professionals of the Thrombosis Service. There was no significant difference between group 1 and 2 in usage of the platform during the three time periods (0-6 months: mean 20.75 , SD 5.20 , $F_{1,109}$ =0.091, p=0.764; 6-12 months: mean 13.00, SD 7.0, $F_{1,109}$=0.029, p=0.866; 12-18 months: mean 12.5, SD 7.39, $F_{1,109}$=1.28, p=0.260).

Discussion

In the present study, no differences were found in therapeutic control and usage of the platform between anticoagulation self-management patients trained by e-learning and by group training. Moreover, the clinical results for self-management patients were similar to those of patients receiving regular care. Therefore, we conclude that, with adequate training through e-learning or group training, self-management is safe and reliable for a selected proportion of motivated patients receiving VKA. The PORTALS study provides valuable information on different implementation methods of OAT self-management, including eHealth.

Strengths and limitations

This PORTALS study has several strengths. First, the study investigates the effect of different education programs in a situation as close to 'real life' as possible, integrated in a self-management program including eHealth, on clinical outcomes and self-management skills. The study also adds evidence to the existing body of knowledge on implementation of eHealth; this is important because local political/financial factors have a major impact on successful integration of eHealth in daily practice and because self-management is important for patients who will use VKAs in the future [33].

This study also has limitations. First, a randomized controlled trial (RCT) was not feasible in our setting of an implementation design in a real-life healthcare system with patients who have differing demands. Instead, an observational study was considered the best option for our context, i.e. patients cannot be denied or forced to start with self-management. Furthermore, self-management skills imply behavioral changes. However, behavioral changes require time, whereas the study period was restricted to 18 months. This study also has limitations typically associated with eHealth trials. For example, as patients were free to volunteer, bias might have occurred in our study groups. Users were self-selected and were, presumably, motivated to use the education program (including the web-based platform) as would be expected in a real-life setting. Of the 1632 invited OAT patients, 247 patients (15%) were willing to participate and provided informed consent. However, only 137

patients (8.4% of invited patients) wanted to participate in the self-management groups and were randomized; other studies have a similar low recruitment rate for self-management trials [34]. This phenomenon might have affected the measurability of differences and might also reduce differences between the groups. The high number of participants lost to follow-up in our study ("law of attrition"; the phenomenon of participants stopping usage) is a common finding in eHealth evaluations and one of the fundamental and methodological challenges in the evaluation of eHealth apps [35]. The loss to follow-up is high with a risk of biased results due to user bias; therefore, these results are only applicable for users of eHealth.

The total population of the Thrombosis Service showed a lower percentage of men than the participants of the present study, although the distribution of indications/medication was similar. In the total population, the percentage of severe complications was low (bleedings 2%, thromboembolism 0.8%); during our study period the percentage of complications was also low (group e-learning =3.2%; group training =1.4%; group usual care =0%), indicating a high quality of thrombosis care.

During the process of inviting patients for the PORTALS study, we asked their reasons for not participating (main reasons were: not having a computer/internet, no digital skills, the effort of participating, and their high level of satisfaction with usual care). The group with usual care differed significantly from the self-management groups on several baseline characteristics: i.e. patients in usual care were older, had a lower education level, and fewer of them had paid work. Also, they had a lower GSES and EQ5D, and made less use of acenocoumarol. Patients in the total population of the Thrombosis Service, and in the usual care group, might have different wishes and expectations towards care than patients that chose for a self-management program; i.e. self-management programs are suitable for patients that are highly motivated and have skills for self-management tasks.

Finally, to measure a significant difference in therapeutic control, 72 patients were needed in each group. Although these numbers were not entirely met in group 1 (e-learning), analysis of the groups should be sufficiently powered to detect relevant differences. In addition, the high number of INR data points collected before and after the intervention has a substantial impact on the strength of the design and the multilevel linear analysis.

Due to these limitations, caution is required when generalizing our results to general practice. However, the practical applicability of our results for other specialized OAT centers is positive, i.e. the

study provides practical insight into successful implementation of self-management programs consisting of high-quality training and usage of a patient platform.

Interpretation of findings

No overall significant differences in therapeutic control were found between the three groups; also, there was no difference in therapeutic control between the group with e-learning and group training. Therapeutic INR control was good in all groups; in the last 6 months of the intervention period, all groups spent around 58% of time within the narrow therapeutic range 2-3 and 83% of time within the therapeutic range 2-3.5; this indicates high quality and is comparable to other studies [34] [36]. Anticoagulation control levels around 60% for TTR of INR range 2-3 are considered safe [36] [37] [38]. In studies conducted outside specialized care facilities in several different regions, TTR ranged from 40-70% [13]. The national guidelines for the INR range changed during the last 6 months of our PORTALS study; this had a negative impact on the TTR during our last measurement period. Complication rates also compared favorably with international data; our overall adverse event rate was low compared to other studies [39] [40] [41].

In comparison to literature, the baseline quality of OAT management in the present study can be considered high in all groups; therefore, further improvement through a self-management program including education was difficult to achieve and the outcomes in the groups remained the same. Finally, both training methods were comparable on the effect of anticoagulation control; for patients and healthcare professionals this means that a good e-learning program is a good alternative for labour intensive group trainings. Based on our study, we recommend considering self-management programs supported by e-learning as the preferred plan of action for self-management for anticoagulation patients. Furthermore, self-management with an e-learning component is suitable for motivated patients with sufficient digital skills; in our opinion, regular anticoagulation care needs to remain available for the rest of the population.

Self-efficacy and educational level of users had no impact on therapeutic control for the different implementation methods. The construct of perceived self-efficacy reflects an optimistic self-belief [31]; a correlation can be understood based on the belief that one can perform a novel or difficult task, or cope with adversity (indicating a higher self-efficacy). In the present study, self-efficacy was comparable to that in a healthy Dutch population [42] [43].

The practical value of the Portavita portal is very high for patients, because of the functionalities of self-monitoring, self-dosage and digital advice from professional healthcare providers. Because

patients use the self-management program, regular visits to medical facilities are unnecessary. Patients can manage their anticoagulation in their own time and in their own chosen place. Thus, using the self-management program gives them (extra) freedom; this might be a strong motivating factor for using the program. Also, the training programs were sound and sustainable during the entire study period, probably stimulating patients to persevere with their self-management program. Moreover, e-learning and group training led to the same usage and, therefore, the same self-management skills. Therefore, we conclude that our e-learning and group training provide a good start for OAT patients that voluntarily start with a self-management program including eHealth.

Self-management programs with eHealth technologies for chronic conditions can be used to enhance self-management and revise the Chronic Care Model; patients who actively participate in their care achieve valuable and sustained improvement in wellbeing [44] [45]. In many eHealth studies, use of a Personal Health Record or self-management platform can promote an informed/activated patient and augment the Chronic Care Model for self-management support and productive interactions; even though a direct dosage-effect relation (usually analyzed in a classical RCT) is not common in eHealth [46]. Self-management programs with good training and practical eHealth platforms have the potential to make chronic care personalized in a blended care model; every patient needs a different approach for optimal therapeutic control. Healthcare providers need to embrace a different role and release tight protocols [47]. Individual patients have different expectations and wishes, which should be a topic of conversation with each patient. The general scientific basis for self-management applies perfectly to anticoagulation patients, which is confirmed in our study.

More studies are needed (preferably with larger sample groups, and including non-users) to gain more insight into the preferences of various patient groups, as well as the related costs.
The substantial workload generated by integrating a web-based platform in an OAT self-management program emphasizes the importance of piloting and assessing workforce implications for OAT management centers. The present results provide additional insight into the organizational aspects of the implementation of education programs into a self-management program with a platform, including the need to educate and coach patients in the use of web-based platforms.

Conclusion

Our main finding is that there were no differences in therapeutic control and usage of a supporting eHealth platform between anticoagulation self-management patients trained by e-learning and by group training. Moreover, we found that clinical results for self-management patients are

comparable to those of patients receiving usual care. We conclude that with appropriate and sound training through e-learning or group training, self-management is safe and reliable for a selected proportion of motivated patients receiving oral anticoagulation treatment. The PORTALS study provides valuable information on different implementation methods of oral anticoagulation self-management, including eHealth.

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Data sharing

Data will be made available for sharing where available and appropriate.

Transparency declaration

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.
All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Ethics and consent to participate

This study is conducted according to the principles of the Declaration of Helsinki (version 59, 2008) and in accordance with the Medical Research Involving Human Subjects Act (WMO). Participants were only included in the study after written informed consent was received. The Medical Ethics Committee of the LUMC approved this study (Reference No. P12.278).

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships

with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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Author's contributions

ET is the principle investigator and contributed to all aspects of the research. NV assisted on all aspects. MK assisted on the statistical analysis and is responsible for revising the manuscript several times. LH is responsible for revising the manuscript several times. IT is responsible for the acquisition of data and revising the manuscript several times. MN is responsible for revising the manuscript. NC is responsible for the concept, design, and for revising the manuscript. All authors read and approved the final manuscript.

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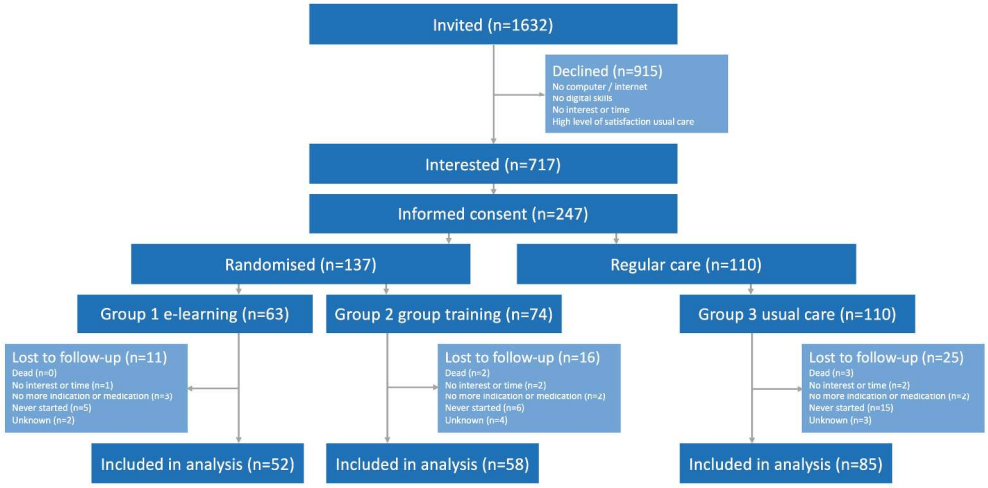


Figure 1. Flowchart of the PORTALS study

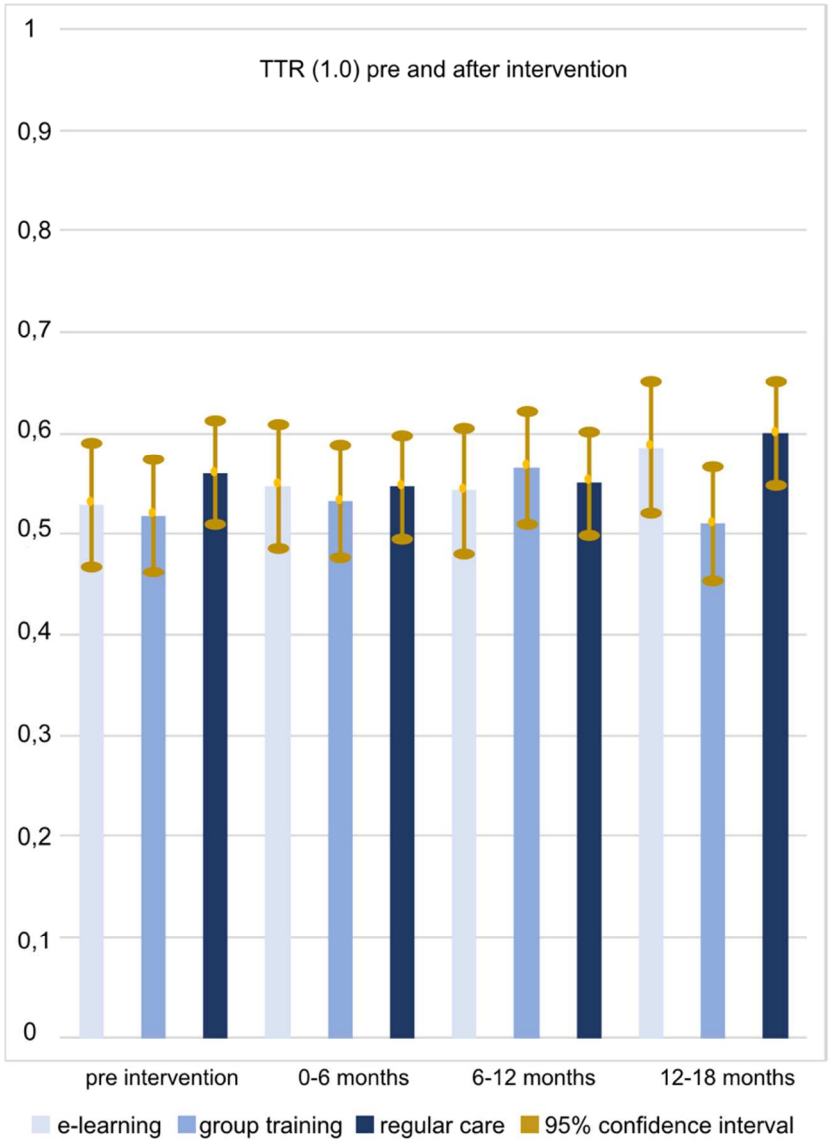


Figure 2A. Health status based on time in therapeutic (TTR) (for INR range 2-3) for the three groups.

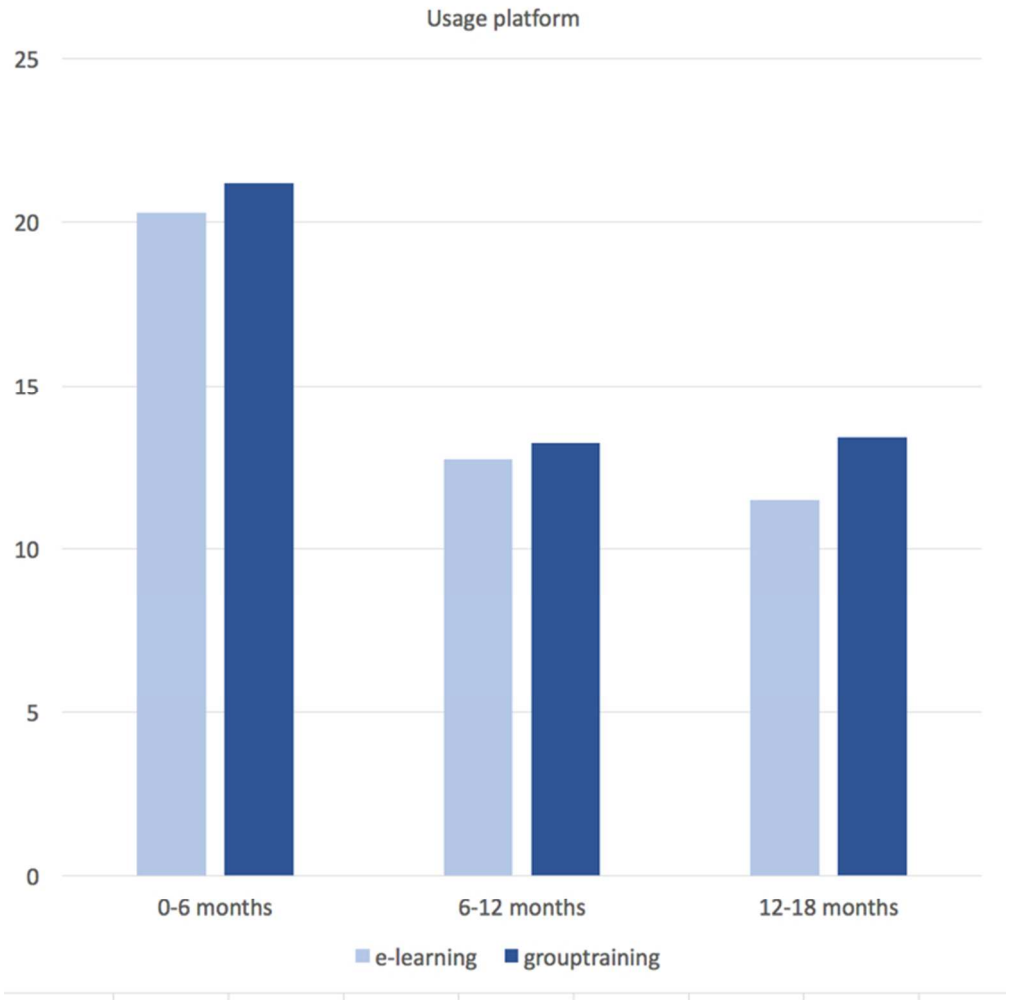
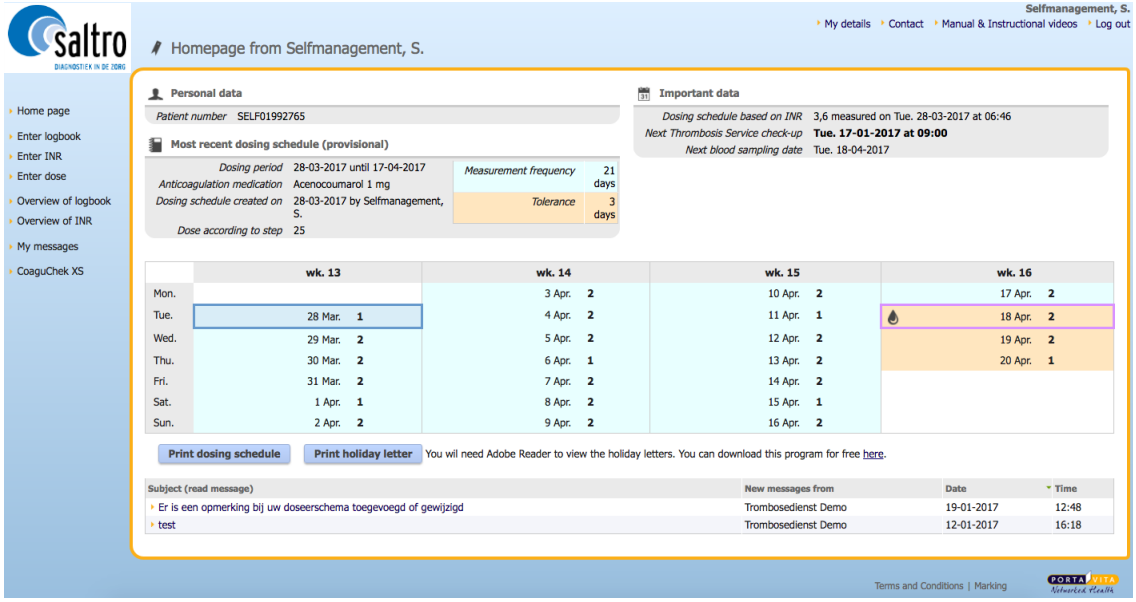
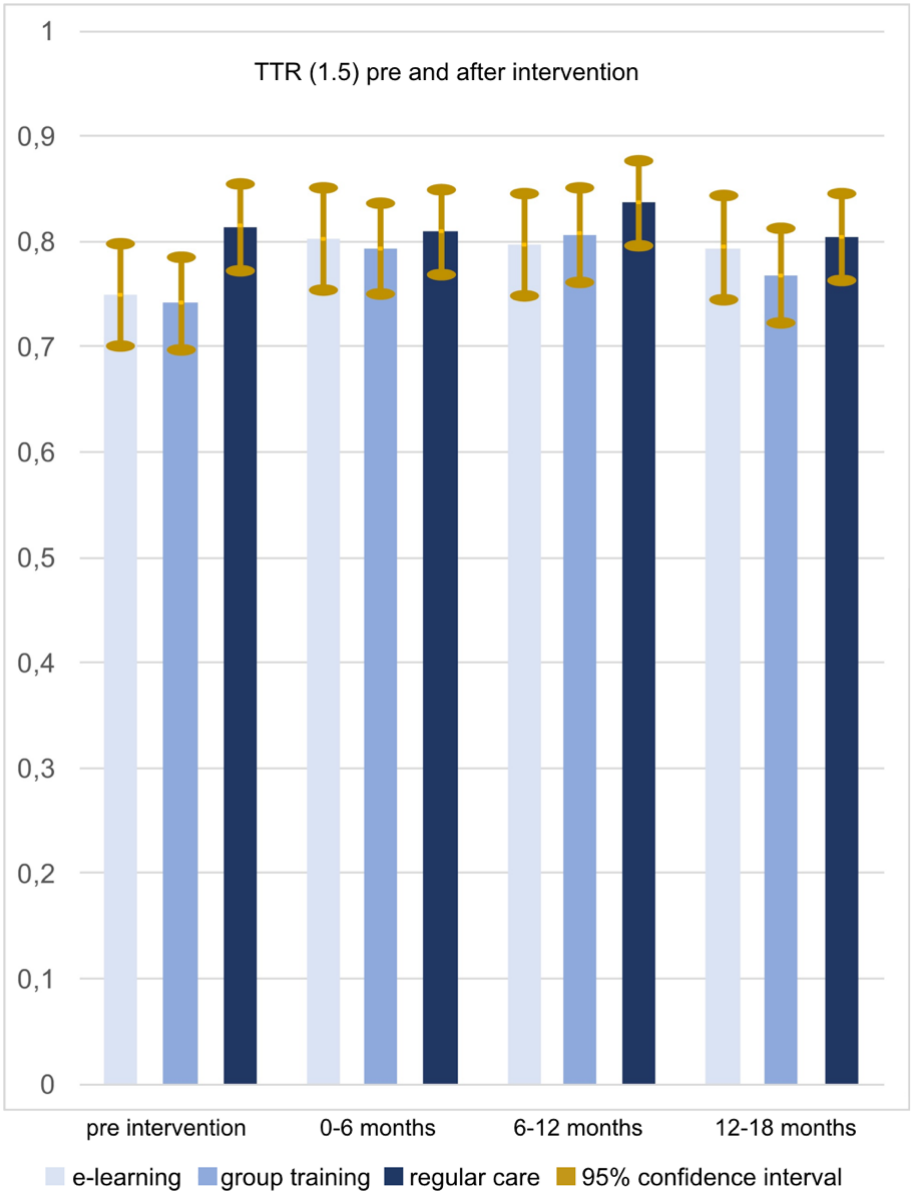


Figure 3. Usage of the platform in group 1 and group 2 after start of the intervention.

Appendix 1: E-learning anticoagulation



Appendix 2: Patients' self-management web portal homepage



Appendix 3: Health status based on time in therapeutic (TTR) (for INR range 2-3.5) for the three groups. Figure 2B shows TTR values using the INR 2-3.5 in the three groups, 6 months before the intervention and in the 3 x 6-month periods after the intervention. Analysis of the three groups showed that the TTR values differed significantly over time (p=0.017). No significant differences were found in TTR between the groups (p=0.163) or between the groups over time (p=0.545).

Analysis of the two self-management groups showed significant differences in the TTR values between the four time periods (i.e. pre- and postintervention) (p=0.008). There were no significant differences in TTR between group 1 and 2 (p=0.721) or between the groups over time (p=0.825).

Equivalent health status for e-learning, group training self-management or usual care in oral anticoagulation patients: a parallel cohort design in the PORTALS Study

STROBE statement, checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract		
	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract – Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found – Page 2
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported – Page 3 (Introduction)
Objectives	3	State specific objectives, including any prespecified hypotheses – Page 4 (Introduction)
Methods		
Study design	4	Present key elements of study design early in the paper – Page 5/6 (Study design) + figure 1
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection – Page 5 (Study design) + reference 28
Participants	6	(*a*) *Cohort study*?Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up – Page 6 (Participants) + reference 28
		(*b*) *Cohort study*?For matched studies, give matching criteria and number of exposed and unexposed Participants were not matched + figure 1
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give

	Item No	Recommendation
		diagnostic criteria, if applicable – Page 8/9 (Outcome measures and determinants)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). – Page 8/9 (Outcome measures and determinants) Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias – Page 9 (Sample size and statistical methods)
Study size	10	Explain how the study size was arrived at – Page 9 (Sample size and statistical methods)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why – Page 8/9 (Outcome measures and determinants)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding – Page 9 (Sample size and statistical methods)
		(*b*) Describe any methods used to examine subgroups and interactions – Page 9 (Sample size and statistical methods)
		(*c*) Explain how missing data were addressed – Page 9 (Sample size and statistical methods)
		(*d*) *Cohort study*?If applicable, explain how loss to follow-up was addressed – Page 9 (Sample size and statistical methods)
		(*e*) Describe any sensitivity analyses Not applicable.
Results		
Participants	13*	(*a*) Report numbers of individuals at each stage of study?eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed – Page 9/10 (Results)
		(*b*) Give reasons for non-participation at each stage – Page 10/11 (Baseline characteristics of study participants)
		(*c*) Consider use of a flow diagram Figure 2.
Descriptive data	14*	(*a*)Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders – Page 10/11 (Baseline characteristics of study participants)

	Item No	Recommendation
		(*b*) Indicate number of participants with missing data for each variable of interest – Page 10/11 (Baseline characteristics of study participants) + Table 3
		(*c*) *Cohort study*?Summarise follow-up time (eg average and total amount) – Page 8/9 (Outcome measures and determinants)
Outcome data	15*	*Cohort study*?Report numbers of outcome events or summary measures over time – Page 12/13 (Usage of the platform)
Main results	16	(*a*) Report the numbers of individuals at each stage of the study?eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed – Page 9/10 (Results)
		(*b*) Give reasons for non-participation at each stage – Page 9/10 (Results)
		(*c*) Consider use of a flow diagram Figure 2.
Other analyses	17	Report other analyses done?eg analyses of subgroups and interactions, and sensitivity analyses Page 12 (Health status before and after intervention/Educational level and GSES)
Discussion		
Key results	18	Summarise key results with reference to study objectives – Page 13 (Discussion)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias – Page 13/14 (Strenghts and limitations)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence – Page 14/15 (Interpretation of findings)
Generalisability	21	Discuss the generalisability (external validity) of the study results – Page 16 (Interpretation of findings)
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based – Page 17 (Funding)

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross sectional studies.

The STROBE checklist is best used in conjunction with the explanation and elaboration article.[18-20] This article and separate versions of the checklist for cohort, case-control, and cross sectional studies are available at www.strobe-statement.org.

BMJ Open

Effect of a combined education and eHealth program on the control of oral anticoagulation patients (PORTALS study): a parallel cohort design in Dutch primary care

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Secondary Subject Heading:	Health informatics, Medical education and training, General practice / Family practice
Keywords:	self-efficacy, eHealth, TTR, self-management, thrombosis, oral anticoagulation

Effect of a combined education and eHealth program on the control of oral anticoagulation patients (PORTALS study): a parallel cohort design in Dutch primary care

Esther PWA Talboom-Kamp MD MBA[1 2], Noortje A Verdijk MSc PhD[1 2], Marise J Kasteleyn MSc PhD[1], Lara M Harmans MSc[2], Irvin JSH Talboom[3], Mattijs E Numans MD PhD[1], Niels H Chavannes MD PhD[1]

[1] Leiden University Medical Centre, Public Health and Primary Care Department
P.O. Box 9600, 2300 RC Leiden, the Netherlands

[2] Saltro Diagnostic Centre
Mississippidreef 83, 3565 CE Utrecht, the Netherlands

[3] Zorgdraad Foundation
Wijnand van Arnhemweg 54, 6862XN Oosterbeek, the Netherlands

Corresponding author

EPWA (Esther) Talboom-Kamp MD MBA
Saltro Diagnostic Centre
Mississippidreef 83
3565 CE Utrecht
The Netherlands
Telephone: +31-30-2361170
Fax: +31-30-2361172
E-mail: e.talboom@saltro.nl

Abstract

Objectives To analyze the effect on therapeutic control and self-management skills of the implementation of self-management programs, including eHealth by e-learning versus group training.

Setting Primary Care Thrombosis Service Center.

Participants Of the 247 OAT patients, 63 started self-management by e-learning, 74 self-management by group training, and 110 received usual care.

Intervention and methods Parallel cohort design with two randomized self-management groups (e-learning and group training) and a group receiving usual care. The effect of implementation of self-management on time in therapeutic range (TTR) was analyzed with multilevel linear regression modeling. Usage of a supporting eHealth platform and the impact on self-efficacy (Generalized Self-Efficacy Scale; GSES) and education level were analyzed with linear regression analysis. After intervention, TTR was measured in 3 time periods of 6 months.

Main outcome measures i) TTR, severe complications ii) usage of an eHealth platform iii) GSES, education level.

Results Analysis showed no significant differences in TTR between the three time periods (p=0.520), the three groups (p=0.460) or the groups over time (p=0.263). Comparison of e-learning and group training showed no significant differences in TTR between the time periods (p=0.614), the groups (p=0.460) or the groups over time (p=0.263). No association was found between GSES and TTR (p=0.717), or education level and TTR (p=0.107). No significant difference was found between the self-management groups in usage of the platform (0-6 months p=0.571; 6-12 months p=0.866; 12-18 months p=0.260). The percentage of complications was low in all groups (3.2%; 1.4%; 0%).

Conclusions No differences were found between OAT patients trained by e-learning or by a group course regarding therapeutic control (TTR) and usage of a supporting eHealth platform. The TTR was similar in self-management and regular care patients. With adequate e-learning or group training, self-management seems safe and reliable for a selected proportion of motivated VKA patients.

Trial Registration – NTR3947

Keywords – oral anticoagulation; TTR; eHealth; self-management; self-efficacy; e-learning; thrombosis; self-monitoring.

Article summary

Strengths and limitations of this study

- This study investigates the effect of different education and eHealth programs in a situation as close to 'real life' as possible;
- The pragmatic study design will increase the applicability of the findings;
- The combination of clinical and usage data collection will give a deeper comprehension of the results;
- A potential limitation is that patients were free to volunteer, which might have caused bias in our study groups.

Introduction

Venous thromboembolism (VTE) and atrial fibrillation (AF) are common causes of mortality and morbidity, with rising prevalence and medical costs [1] [2] [3]. Oral anticoagulation therapy (OAT) reduces thromboembolic events in AF, prosthetic heart valves, acute myocardial infarction and other conditions, and is an effective treatment for VTE [4] [5] [6]. The major risks of OAT are bleeding complications, with a rate of major bleeding among long-term users of vitamin K antagonists (VKAs) of 1.5-5.2% per year [7] [8] [9]. There is a narrow therapeutic range for VKA, expressed as the international normalized ratio (INR) with an optimal intensity, related to a low rate of events, between 2.5 and 4.9 [10] [11]. This is relevant, as patients have considerable difficulty in maintaining adequate adherence to VKA regimens, with a significant effect on anticoagulation control [12]. Structured monitoring and coaching of patients using VKA is essential. This may be carried out by specialized centers in primary care or in hospitals [13]. Alternatively, patients might choose to self-manage their VKA monitoring. In the case of VKA, self-management includes monitoring INR values by patients (self-monitoring) and, as a possible next step, self-adjustment of the medication dosage (self-dosage). Nowadays, patients are usually supported by improved eHealth supported self-management programs [14] with more freedom, improved quality of life and self-efficacy, and less burden of specialized centers [15] [16]. Research shows a reduction of thromboembolic events and in all-cause mortality for patients with self-management [17], due to the fact that patients have greater responsibility, increased awareness, commitment and interest in their condition [18].

Adequate self-management is important for all patients with OAT to improve adherence to medication, irrespective of the type of anticoagulation medicine they use [19] [20] [21]. The basic principle of self-management is behavioral change, which is necessary to improve the quality of life of patients and the primary outcomes of their health and disease [22]. Research on chronic diseases such as diabetes [23], COPD [24], and heart failure [25] has shown that aspects such as self-efficacy (belief in one's capabilities to organize and execute the course of action required to produce given attainments), educational level, socioeconomic status (SES), age and sex are influencing factors in successful self-management and predictors in eHealth usage [26].

As education is the basic approach in the development of self-management skills, the strategy used to implement educational support is expected to affect the individual level of self-management and, thereby, clinical outcomes. To test this hypothesis, we designed the PORTALS study. The aim of this study was to analyze the effect on anticoagulation control of an intervention consisting of an education program in combination with the use of an online self-management portal. The general

definition of self-management is the individual's ability to manage the symptoms, treatment, physical and psychosocial consequences and life style changes inherent in living with a chronic condition [27]; in line with this definition, both self-monitoring and self-dosage of medication are considered important self-management skills in the PORTALS study.

Methods

Study design

For the PORTALS study, we designed a quality improvement intervention and compared strategies in an implementation study [28]. Two methods were developed to train long-term VKA patients of the Saltro Thrombosis Service (outpatient anticoagulation clinic and laboratory) in self-management routine care. Using this design, we aimed to examine the influence of the training strategy on clinical outcomes and usage of the supporting eHealth platform. Full methodological details are reported elsewhere [29]; Table 1 presents an overview of the study design.

Table 1. Overview of the study design: details of groups 1, 2 and 3

	Saltro Thrombosis Service Centre		
	Self-Management		Usual Care
Patients	Group 1	Group 2	Group 3
	#72	#72	#72
Instruction	**E-Learning** Disease-specific knowledge Self-testing skills Use of the web-portal (voluntary) Self-adjustment of medication	**Group Course** Disease-specific knowledge Self-testing skills Use of the web-portal (voluntary) Self-adjustment of medication	**Basic Short Training**
Platform	Self-management	Self-management	

A parallel cohort design was used to investigate determinants of optimal implementation of self-management by comparing two different training methods. After inclusion, participants were randomly divided into subgroups: one group was trained and educated by e-learning (group 1) and the other group received face-to-face group training (group 2). Patients unable or unwilling to dose

their medication were free to continue with only self-monitoring. Patients who did not wish to start with self-management were invited to participate in the non-self-management group, i.e. a parallel cohort group receiving usual care (group 3). Group 3 provided valuable information about the patients who were unable/unwilling to use an online supported self-management program.

Based on our parallel cohort design, comparison between e-learning and group training for self-management (group 1 and 2) and non-self-management patients (group 3) is applicable, considering the specific conditions in the choice of the statistics.

Participants

The present study focused on patients of the Saltro Thrombosis Service who voluntarily chose to start with self-management. The inclusion criteria for patients to start with self-management were a long-term indication for anticoagulants, internet access, and stable INR values (at least three INR values in succession must be within therapeutic range). Patients who met the criteria for self-management were approached for participation in the study. Because self-management (including eHealth) is already an option for patients of the Saltro Thrombosis Service, the group training was also open to patients who were not willing to participate in the study. The e-learning was reserved for participants of the present study, as this was a new implementation method. All patients provided written informed consent before participation in the study.

Patient involvement

Patients were neither involved in the design, nor in defining research questions and outcome measures of the study; however, they were actively involved in the development of the self-management platform Portavita. To maximize the involvement of patients we did not randomize the intervention groups (self-management and usual care); we chose a recruitment design in which patients of the Thrombosis Service voluntarily chose to start with self-management. During the study patients could give feedback on the intervention and on the self-management platform; their satisfaction was continuously monitored. Feedback from patients made it possible to optimize their care. All patients will be informed about the results of this study.

Recruitment of patients and non-participation

Patients of the Saltro Thrombosis Service who received regular care without a self-management program were eligible for recruitment. In 2013, 8950 patients received usual care from the Saltro Thrombosis Service of which 85% had a long-term indication. From June 2013 onward, a random

selection of 1632 patients was approached for participation in the present study using three methods, i) information and invitation by letter, ii) personal invitation by specialized nurses, and iii) invitation by telephone. Patients who did not wish to start with self-management were invited to participate in a parallel cohort group receiving usual care (group 3), thereby providing valuable information about non-participants. Baseline characteristics of all regular patients of the Saltro Thrombosis Service also provided valuable information about non-participants.

Intervention

The intervention in group 1 and 2 consisted of a training program in combination with the use of an online self-management portal called Portavita. In group 1, patients used an e-learning that was specifically designed for the PORTALS study (Multimedia Appendix 1).

Table 2 summarizes the programs in all groups: the e-learning modules in group 1, the group training modules in group 2, and the basic training in group 3. In group 1 the training was provided by e-learning that started with a personal login procedure and an online instruction; the interim control and quality checks were carried out by specialized nurses of the Thrombosis Service. The group course in group 2 was carried out by specialized and expert healthcare professionals. Both training methods had the same content, but were offered in a completely different manner.

Table 2. Training methods in group 1, 2 and 3.

Group 1	Group 2	Group 3
General education (e-learning) about anticoagulation + test Selftesting device Training (e-learning) selftesting + use of web portal Three months of e-learning + selftesting	Group course with training selftesting + use of web portal Three weeks practice at home Group course about anti coagulation Three months of training at home	Basic training
Selftesting device	Selftesting device	Venipuncture at home or in facilities

Control and quality check by nurse Continuing self-management program + Control and quality check by nurse every six months	Control and quality check by nurse Continuing self-management program + Control and quality check by nurse every six months	Written instructions by thrombosis doctor

In the PORTALS study, the online self-management portal used is called Portavita (Multimedia Appendix 2). This application combines a patient portal and a healthcare provider portal. The healthcare portal leaves space for the OAT protocol, medication records, and information about complications. The Portavita Anticoagulation Self-management patient portal has become widely accepted; it provides patients with a diary tool for self-monitoring and self-dosage, education, it also allows personal notes, and healthcare professionals can send advice and notes to the patient. It implies that the patient analyzes a drop of blood using a home INR monitor. The patient can access the web-based patient portal to enter the INR and specific information for the health professional (intervention, bleeding, change in medication, vacation, etc.). Clinically validated inbuilt algorithms provide advice regarding the next dose and test interval. The only things needed are an internet connection and a device like a PC, tablet or smartphone. When logging on (username + password) for the first time to Portavita, every user was directed to the homepage. From there, users could access all functionalities of the portal. The logon procedure of this portal is based on Dutch security legislation and guidelines (the Dutch Personal Data Protection Act).

Data collection

INR values, thromboembolic events, bleedings, medication and indication were monitored and registered continuously by patients in the portal and by professionals of the Saltro Thrombosis Service. We measured the INR, complications and medication during a period of 6 months before and 18 months after starting the intervention (i.e. 24 months in total). The data collection also consisted of questionnaires (at baseline, and after each 3 x 6-month period) to measure the determinants and outcomes. Patients of group 1 and 2 received these questionnaires by e-mail, and patients in group 3 by e-mail or by post. In addition, the number of self-tests and use of the portal were continuously registered in the portal. Data on the total population of the Saltro Thrombosis Service were also collected.

Outcome measures and determinants

The primary outcome of this study was therapeutic control expressed as the INR control over time and severe complications (bleedings and thromboembolic events). To summarize the INR control over time, the percentage of time in therapeutic range (TTR) of INR was used, calculated with the Rosendaal method [30]. TTR values were calculated for two INR ranges (INR 2-3 and INR 2-3.5) because different calculations are used in Dutch and in international guidelines. TTR was measured at four moments: at 6 months before intervention, and at 3 x 6-month periods (total of 18 months) after starting the intervention. Serious complications were defined as those needing treatment or medical evaluation. An independent thrombosis specialist was responsible for classifying serious complications at the end of the trial. The total follow-up period for all these measures was 24 months.

Furthermore, the self-management skills of participants were evaluated. Self-management skills were defined as usage of the self-management platform, reflected as the amount of login sessions. Self-monitoring and self-dosage are registered within the same login session. The usage counts were analyzed. The determinants were self-efficacy and socio-demographic characteristics. Self-efficacy was measured at baseline using the Generalized Self-Efficacy Scale (GSES), with items scored on a four-point scale with a higher score reflecting higher self-efficacy [31]. Socio-demographic characteristics were assessed by an online questionnaire addressing the following characteristics: age, gender, education level, marital status, working status (labor), and quality of life (QoL), which was assessed using the EuroQol-5D (EQ-5D) and displayed at baseline. The EQ-5D is a 5-item questionnaire with a higher score reflecting a higher QoL.

Sample size and statistical methods

To detect a relevant effect of the new implementation strategy of e-learning or group training (>5%) [32] at a power 80% and α=0.05, we calculated that a sample size of 63 patients was required per group. Considering a 15% drop out, 72 (63/0.85) patients were needed per study group. Baseline characteristics between the three groups were explored using Chi-square tests and Kruskal-Wallis tests.

To investigate the effect of the different implementation methods of training versus the parallel cohort group on TTR, multilevel linear regression modeling (mixed models) was used. First, TTR outcomes were compared between the three groups. A second (mixed models) analysis was used to compare the difference in effect between e-learning and group training (group 1 vs. group 2) on TTR.

The variable TTR was included as outcome in the model. The periods of TTR measurements (time), the group and the interaction term (time*group) were included as predictors.
Both analyses were adjusted for age and gender.

To examine the impact of GSES and education on the effect of the different implementation methods, multiple linear regression analyses were performed with TTR at time point 3 as outcome, and GSES and education as predictors. Analyses were adjusted for age and gender.
A linear regression analysis was used to analyze usage (mean number of login sessions) of the portal Portavita in group 1 and 2.

Results

A total of 1632 VKA patients of the Saltro Thrombosis Service were invited to participate, of which 56% (n=915) declined (Figure 1). Patients were invited in three different ways: by letter (n=475), by personal invitation during a visit to the Thrombosis Service (n=692) and by telephone (n=465). 717 patients were interested in participation in the study; 247 patients eventually signed an informed consent. During the process of inviting patients for the PORTALS study, patients were asked about their reasons for not participating: the main reasons were not having a computer or internet, no digital skills, the effort of participating in a trial, and their high level of satisfaction with usual care.

Participants were included in the study only after providing written informed consent but, because some patients failed to do this, 247 participants were finally included. Of these, 110 continued to receive regular care (group 3) and 137 patients were randomly divided into group 1 and 2 using a computer program. After randomization, 63 patients were included in group 1 (e-learning) and 74 in group 2 (group training). Figure 1 summarizes the recruitment process, including the reasons for loss to follow-up.

Characteristics of the total population of the Thrombosis Service

The characteristics of all VKA patients of the Saltro Thrombosis Service in 2015 are shown in Table 3.

Table 3. Clinical characteristics of the population of the Saltro Thrombosis Service.

Total patients N	11132

Male N (%)	6009 (54.0)
Self-management N (%)	1986 (17.8)
Male self-management N (%)	1260 (63.4)
Medication	
Acenocoumarol N (%)	8360 (75.1)
Phenprocoumon N (%)	2761 (24.8)
Warfarin N (%)	11 (0.1)
Indications	
AF N (%)	7430 (66.8)
Ven thromboembolism N (%)	1673 (15.0)
Artificial valve N (%)	720 (6.5)
Other N (%)	1309 (11.8)
Severe complications	
Major bleedings N (%)	219 (2.0)
Thromboembolism N (%)	85 (0.8)

Baseline characteristics of study participants

Table 4 presents the baseline characteristics of the participants: median age was 66.9 years, and median TTR was 54.7 (for INR range 2-3) and 79.1 (for INR range 2-3.5). Of these patients, 66% had an indication of AF and 77.3% used acenocoumarol as oral anticoagulation medication. No significant differences were found between the three groups for gender (χ^2_2=0.38, p=0.826), TTR (χ^2_2=3.68, p=0.159), indication (χ^2_2=8.33, p=0.215), and marital status (χ^2_2=7.47, p=0.280). The three groups differed significantly in age (χ^2_2=19.96, p=0.000), baseline GSES (χ^2_2=15.08, p=0.001) and EQ-5D (χ^2_2=6.66 , p=0.036), use of medication (χ^2_2=15.23 , p=0.004), education level (χ^2_2=23.72 , p=0.000), and work status (χ^2_2=13.01 , p=0.043) (Table 4).

Table 4. Baseline characteristics of patients with VKA therapy in the PORTALS study

	Group 1	Group 2	Group 3	p-value	Total
N	63	74	110		247
Age in years* [IQR]	65.0[a] [56.2-67.7]	65.8[a] [56.4-70.4]	69.6[b] [64.0-74.9]	0.00**	66.9 [59.5-72.7]
Males N (%)	47 (74.6)	52 (70.3)	81 (73.6)	0.826	180 (72.9)
TTR INR range 2-3 (%)* [IQR]	50.2 [39.1-67.1]	52.9 [39.0-68.6]	57.4 [40.1-75.1]	0.159	54.7 [39.8-70.7]
TTR INR range 2-3.5 (%)* [IQR]	76.3 [67.0-86.0]	77.1 [64.1-85.3]	85.6 [72.0-93.5]	0.159	79.1 [68.2-88.8]

GSES* [IQR]	3.5[a] [3.1-3.8]	3.3[a,b] [3.0-3.7]	3.1[b] [2.9-3.5]	0.001**	3.3 [3.0-3.7]
EQ5D* [IQR]	1.0[a] [0.81-1.0]	0.84[a,b] [0.78-1.0]	0.84[b] [0.78-1.0]	0.036**	0.84 [0.81-1.0]
Indication					
AF N (%)	42 (66.7)	44 (59.5)	77 (70.0)	0.215	163 (66)
Ven thromboembolism N (%)	13 (20.6)	18 (24.3)	11 (10.0)		42 (17)
Artificial valve N (%)	2 (3.2)	3 (4.1)	4 (3.6)		9 (3.6)
Other N (%)	6 (9.5)	9 (12.2)	18 (16.4)		33 (13.4)
Medication					
Acenocoumarol N (%)	51 (81)[a]	64 (86.5)[a]	76 (69.1)[b]	0.004**	191 (77.3)
Phenprocoumon N (%)	10 (15.9)[a]	10 (13.5)[a]	34 (30.9)[b]		54 (21.9)
Warfarin N (%)	2 (3.2)[a]	0 (0)[a]	0 (0)[a]		2 (0.8)
Education level					
Low N (%)	7 (12.1)[a]	13 (19.1)[a]	33 (35.9)[b]	0.00**	53 (24.3)
Medium N (%)	24 (41.4)[a]	32 (47.1)[a]	46 (50.0)[a]		102 (46.8)
High N (%)	27 (46.6)[a]	23 (33.8)[b]	13 (14.1)[c]		63 (28.9)
Marital status					
Married N (%)	49 (84.5)	50 (73.5)	73 (79.3)	0.280	172 (78.9)
Widow N (%)	1 (1.7)	6 (8.8)	4 (4.3)		11 (5.0)
Divorced N (%)	1 (1.7)	6 (8.8)	4 (4.3)		11 (5.0)
Single N (%)	7 (12.1)	6 (8.8)	11 (12.0)		24 (11.0)
Labour					
No paid work N (%)	28 (48.3)[a]	29 (42.6)[a]	39 (42.4)[a]	0.043**	96 (44.0)
Paid work N (%)	19 (32.8)[a]	20 (29.4)[a]	14 (15.2)[b]		53 (24.3)
Household N (%)	8 (13.8)[a]	11 (16.2)[a]	23 (25.0)[a]		42 (19.3)
Incapacitated N (%)	3 (5.2)[a]	8 (11.8)[a]	16 (17.4)[a]		27 (12.4)

***Values are medians and corresponding Interquartile Ranges [IQR]**

**** Between-group differences (P < 0.05) are indicated by ****

Each superscript (a,b,c) letter denotes a subset of sample categories which do not differ significantly from each other at the 0.05 level.

TTR is the therapeutic international normalized ratio (INR) range, GSES is the General Self-efficacy Scale, EQ5D EuroQol five dimensions questionnaire is a standardized instrument for use as a measure of health outcome.

N Missing questionnaires: GSES 29, EQ5D 32, indication 0, medication 0, education 29, marital status 29, labour 29.

Therapeutic control before and after intervention

Figure 2A shows the TTR values using the INR 2-3 in the three groups, 6 months before the intervention and in the 3 x 6-month periods after the intervention; the TTR values using the INR 2-3.5 are presented in Figure 2B (Appendix 3).

Analysis of the three groups showed no significant difference in TTR values over time ($F_{3,631}$=0.755, p=0.520), between the groups ($F_{2,211}$=0.924, p=0.398), or between the groups over time ($F_{6,631}$=1.009, p=0.418).

Analysis of the two self-management groups showed no significant differences in TTR values between the four time periods ($F_{3,378}$ =0.602, p=0.614). Also, no significant differences in TTR were found between group 1 and 2 ($F_{3,378}$ =0.548, p=0.460) or between these two groups over time ($F_{3,378}$ =1.335, p=0.263).

The sensitivity analyses showed that using an INR of 2-3.5, instead of 2-3, had no marked effect on the results, although a significant time effect was found. Results are presented in figure 2B in Appendix 3.

During the 18-month period after the intervention, across all three groups, a total of 3 severe complications occurred (3/247=1.2%): i.e. two muscular bleedings in the e-learning group (2/63=3.2%) and one cerebrovascular accident among patients receiving group training (1/74=1.4%); no complications occurred in the usual care group.

Educational level and GSES

Educational level was not associated with the TTR in the last 6 months ($F_{2,198}$=2.263, p=0.107); education level did not modify the effect of the different implementation methods on TTR ($F_{4,198}$=1.659, p=0.161).

No association was found between the GSES and TTR in the last 6 months ($F_{1,198}$=0.132, p=0.717); GSES did not modify the effect of the different implementations methods on TTR ($F_{2,198}$=1.762, p=0.174).

Usage of the platform

Figure 3 presents the usage by patients in group 1 and 2 (using the logfiles of the Portavita platform) during the 18 months after start of the intervention. Patients logged on to the platform to register

their INR; some also used it to establish their medication dosage or to communicate with healthcare professionals of the Thrombosis Service. There was no significant difference between group 1 and 2 in usage of the platform during the three time periods (0-6 months: mean 20.75 , SD 5.20 , $F_{1,109}$ =0.091, p=0.764; 6-12 months: mean 13.00, SD 7.0, $F_{1,109}$=0.029, p=0.866; 12-18 months: mean 12.5, SD 7.39, $F_{1,109}$=1.28, p=0.260).

Discussion

In the present study, no differences were found in therapeutic control and usage of the platform between anticoagulation self-management patients trained by e-learning and by group training. Moreover, the clinical results for self-management patients were similar to those of patients receiving regular care. Therefore, we conclude that, with adequate training through e-learning or group training, self-management is safe and reliable for a selected proportion of motivated patients receiving VKA. The PORTALS study provides valuable information on different implementation methods of OAT self-management, including eHealth.

Strengths and limitations

This PORTALS study has several strengths. First, the study investigates the effect of different education programs in a situation as close to 'real life' as possible, integrated in a self-management program including eHealth, on clinical outcomes and self-management skills. The study also adds evidence to the existing body of knowledge on implementation of eHealth; this is important because local political/financial factors have a major impact on successful integration of eHealth in daily practice and because self-management is important for patients who will use VKAs in the future [33].

This study also has limitations. First, a randomized controlled trial (RCT) was not feasible in our setting of an implementation design in a real-life healthcare system with patients who have differing demands. Instead, an observational study was considered the best option for our context, i.e. patients cannot be denied or forced to start with self-management. Furthermore, self-management skills imply behavioral changes. However, behavioral changes require time, whereas the study period was restricted to 18 months. This study also has limitations typically associated with eHealth trials. For example, as patients were free to volunteer, bias might have occurred in our study groups. Users were self-selected and were, presumably, motivated to use the education program (including the web-based platform) as would be expected in a real-life setting. Of the 1632 invited OAT patients, 247 patients (15%) were willing to participate and provided informed consent. However, only 137

patients (8.4% of invited patients) wanted to participate in the self-management groups and were randomized; other studies have a similar low recruitment rate for self-management trials [34]. This phenomenon might have affected the measurability of differences and might also reduce differences between the groups. The high number of participants lost to follow-up in our study ("law of attrition"; the phenomenon of participants stopping usage) is a common finding in eHealth evaluations and one of the fundamental and methodological challenges in the evaluation of eHealth apps [35]. The loss to follow-up is high with a risk of biased results due to user bias; therefore, these results are only applicable for users of eHealth.

The total population of the Thrombosis Service showed a lower percentage of men than the participants of the present study, although the distribution of indications/medication was similar. In the total population, the percentage of severe complications was low (bleedings 2%, thromboembolism 0.8%); during our study period the percentage of complications was also low (group e-learning =3.2%; group training =1.4%; group usual care =0%), indicating a high quality of thrombosis care.

During the process of inviting patients for the PORTALS study, we asked their reasons for not participating (main reasons were: not having a computer/internet, no digital skills, the effort of participating, and their high level of satisfaction with usual care). The group with usual care differed significantly from the self-management groups on several baseline characteristics: i.e. patients in usual care were older, had a lower education level, and fewer of them had paid work. Also, they had a lower GSES and EQ5D, and made less use of acenocoumarol. Patients in the total population of the Thrombosis Service, and in the usual care group, might have different wishes and expectations towards care than patients that chose for a self-management program; i.e. self-management programs are suitable for patients that are highly motivated and have skills for self-management tasks.

Finally, to measure a significant difference in therapeutic control, 72 patients were needed in each group. Although these numbers were not entirely met in group 1 (e-learning), analysis of the groups should be sufficiently powered to detect relevant differences. In addition, the high number of INR data points collected before and after the intervention has a substantial impact on the strength of the design and the multilevel linear analysis.

Due to these limitations, caution is required when generalizing our results to general practice. However, the practical applicability of our results for other specialized OAT centers is positive, i.e. the

study provides practical insight into successful implementation of self-management programs consisting of high-quality training and usage of a patient platform.

Interpretation of findings

No overall significant differences in therapeutic control were found between the three groups; also, there was no difference in therapeutic control between the group with e-learning and group training. Therapeutic INR control was good in all groups; in the last 6 months of the intervention period, all groups spent around 58% of time within the narrow therapeutic range 2-3 and 83% of time within the therapeutic range 2-3.5; this indicates high quality and is comparable to other studies [34] [36]. Anticoagulation control levels around 60% for TTR of INR range 2-3 are considered safe [36] [37] [38]. In studies conducted outside specialized care facilities in several different regions, TTR ranged from 40-70% [13]. The national guidelines for the INR range changed during the last 6 months of our PORTALS study; this had a negative impact on the TTR during our last measurement period. Complication rates also compared favorably with international data; our overall adverse event rate was low compared to other studies [39] [40] [41].

In comparison to literature, the baseline quality of OAT management in the present study can be considered high in all groups; therefore, further improvement through a self-management program including education was difficult to achieve and the outcomes in the groups remained the same. Finally, both training methods were comparable on the effect of anticoagulation control; for patients and healthcare professionals this means that a good e-learning program is a good alternative for labour intensive group trainings. Based on our study, we recommend considering self-management programs supported by e-learning as the preferred plan of action for self-management for anticoagulation patients. Furthermore, self-management with an e-learning component is suitable for motivated patients with sufficient digital skills; in our opinion, regular anticoagulation care needs to remain available for the rest of the population.

Self-efficacy and educational level of users had no impact on therapeutic control for the different implementation methods. The construct of perceived self-efficacy reflects an optimistic self-belief [31]; a correlation can be understood based on the belief that one can perform a novel or difficult task, or cope with adversity (indicating a higher self-efficacy). In the present study, self-efficacy was comparable to that in a healthy Dutch population [42] [43].

The practical value of the Portavita portal is very high for patients, because of the functionalities of self-monitoring, self-dosage and digital advice from professional healthcare providers. Because

patients use the self-management program, regular visits to medical facilities are unnecessary. Patients can manage their anticoagulation in their own time and in their own chosen place. Thus, using the self-management program gives them (extra) freedom; this might be a strong motivating factor for using the program. Also, the training programs were sound and sustainable during the entire study period, probably stimulating patients to persevere with their self-management program. Moreover, e-learning and group training led to the same usage and, therefore, the same self-management skills. Therefore, we conclude that our e-learning and group training provide a good start for OAT patients that voluntarily start with a self-management program including eHealth.

Self-management programs with eHealth technologies for chronic conditions can be used to enhance self-management and revise the Chronic Care Model; patients who actively participate in their care achieve valuable and sustained improvement in wellbeing [44] [45]. In many eHealth studies, use of a Personal Health Record or self-management platform can promote an informed/activated patient and augment the Chronic Care Model for self-management support and productive interactions; even though a direct dosage-effect relation (usually analyzed in a classical RCT) is not common in eHealth [46]. Self-management programs with good training and practical eHealth platforms have the potential to make chronic care personalized in a blended care model; every patient needs a different approach for optimal therapeutic control. Healthcare providers need to embrace a different role and release tight protocols [47]. Individual patients have different expectations and wishes, which should be a topic of conversation with each patient. The general scientific basis for self-management applies perfectly to anticoagulation patients, which is confirmed in our study.

More studies are needed (preferably with larger sample groups, and including non-users) to gain more insight into the preferences of various patient groups, as well as the related costs.
The substantial workload generated by integrating a web-based platform in an OAT self-management program emphasizes the importance of piloting and assessing workforce implications for OAT management centers. The present results provide additional insight into the organizational aspects of the implementation of education programs into a self-management program with a platform, including the need to educate and coach patients in the use of web-based platforms.

Conclusion

Our main finding is that there were no differences in therapeutic control and usage of a supporting eHealth platform between anticoagulation self-management patients trained by e-learning and by group training. Moreover, we found that clinical results for self-management patients are

comparable to those of patients receiving usual care. We conclude that with appropriate and sound training through e-learning or group training, self-management seems safe and reliable for a selected proportion of motivated patients receiving oral anticoagulation treatment. The PORTALS study provides valuable information on different implementation methods of oral anticoagulation self-management, including eHealth.

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Data sharing

Data will be made available for sharing where available and appropriate.

Transparency declaration

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.
All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Ethics and consent to participate

This study is conducted according to the principles of the Declaration of Helsinki (version 59, 2008) and in accordance with the Medical Research Involving Human Subjects Act (WMO). Participants were only included in the study after written informed consent was received. The Medical Ethics Committee of the LUMC approved this study (Reference No. P12.278).

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships

with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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Author's contributions

ET is the principle investigator and contributed to all aspects of the research. NV assisted on all aspects. MK assisted on the statistical analysis and is responsible for revising the manuscript several times. LH is responsible for revising the manuscript several times. IT is responsible for the acquisition of data and revising the manuscript several times. MN is responsible for revising the manuscript. NC is responsible for the concept, design, and for revising the manuscript. All authors read and approved the final manuscript.

Figure legends

Figure 1. Flowchart of the PORTALS study.

Figure 2A. Health status based on time in therapeutic (TTR) (for INR range 2-3) for the three groups.

Figure 3. Usage of the platform in group 1 and group 2 after start of the intervention.

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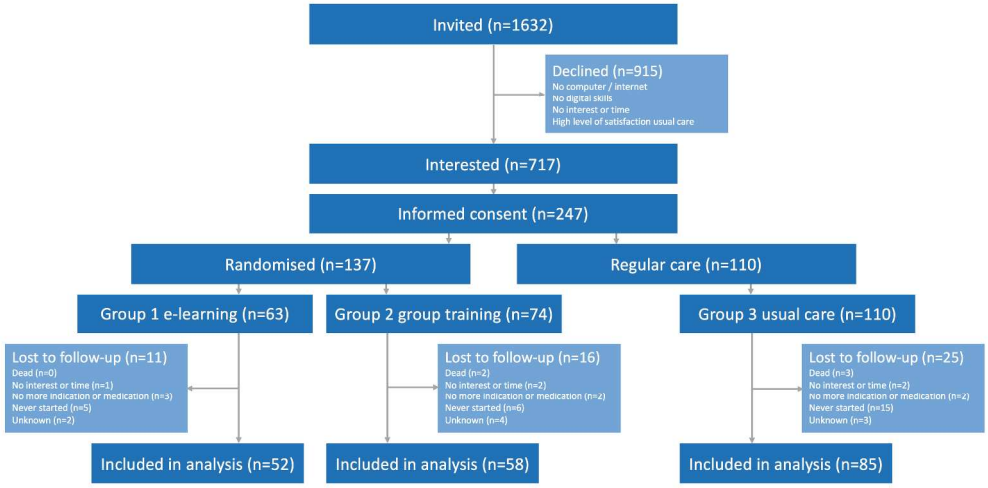


Figure 1. Flowchart of the PORTALS study.

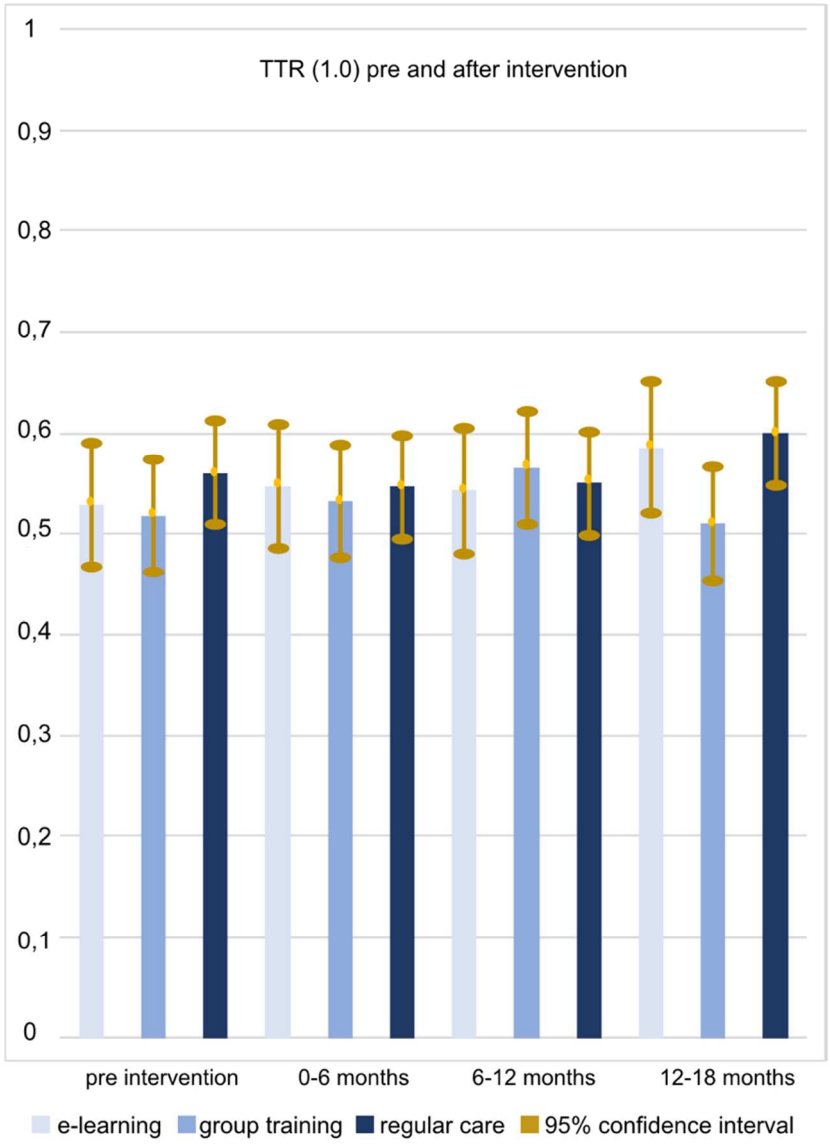


Figure 2A. Health status based on time in therapeutic (TTR) (for INR range 2-3) for the three groups.

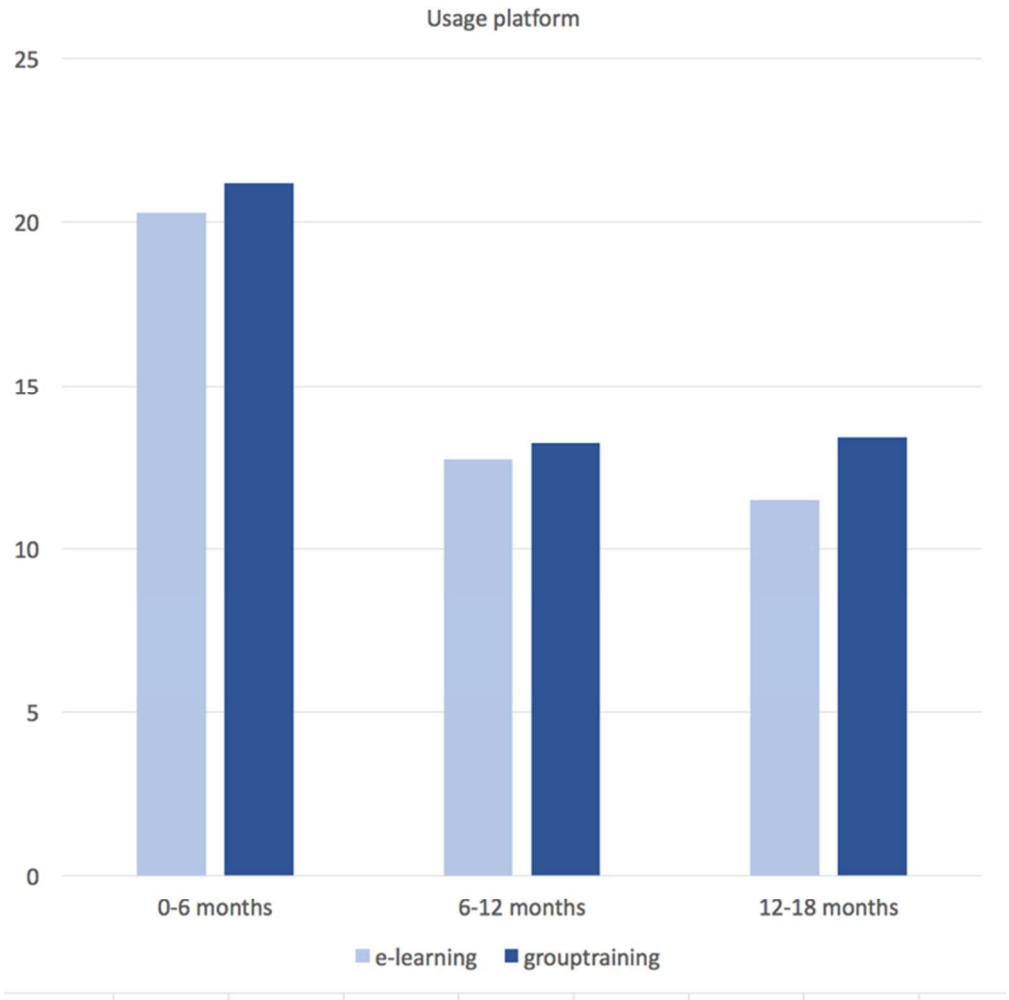
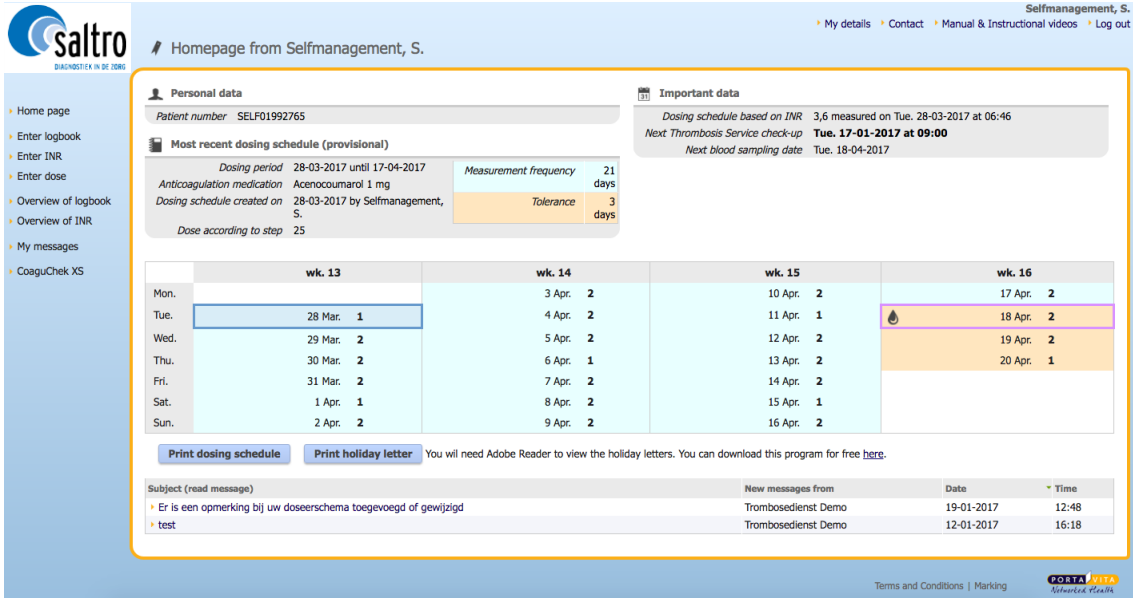
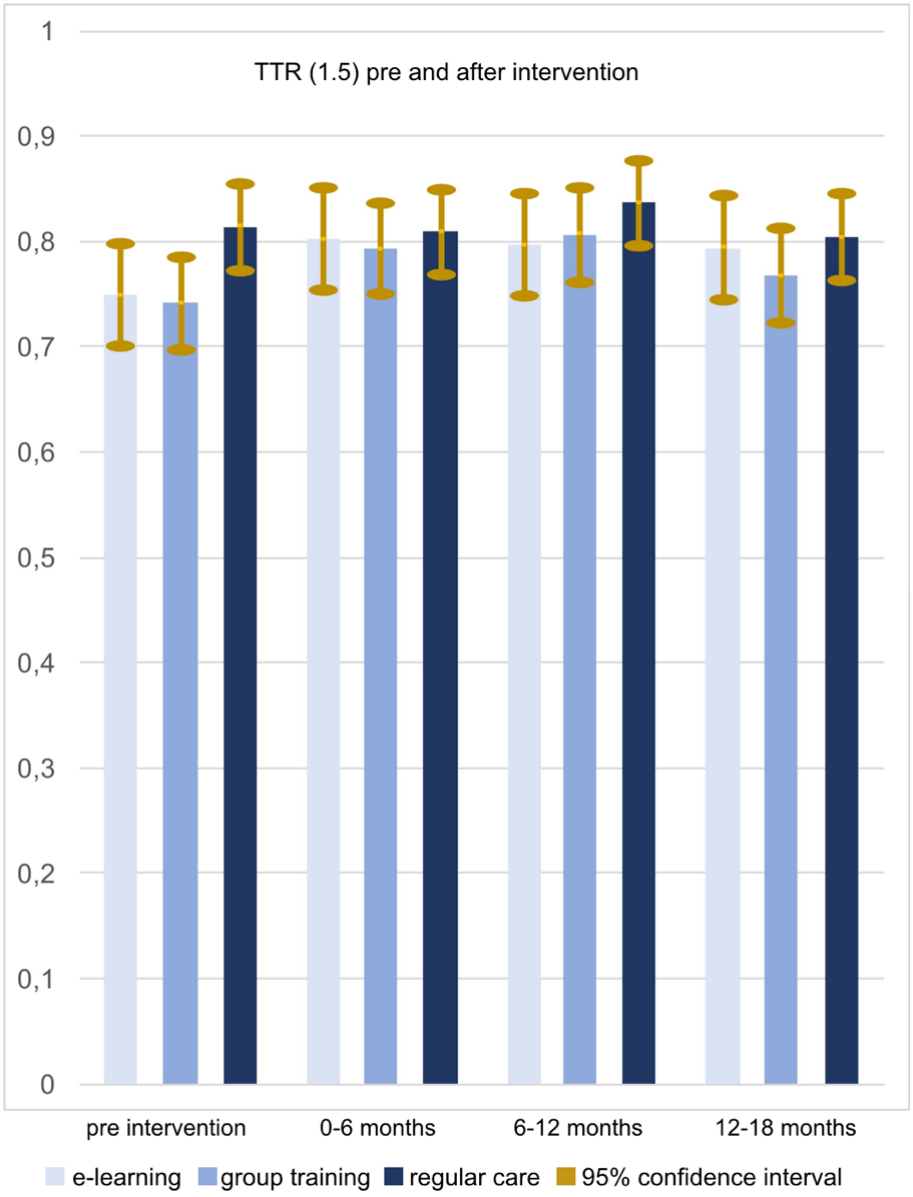


Figure 3. Usage of the platform in group 1 and group 2 after start of the intervention.

Appendix 1: E-learning anticoagulation



Appendix 2: Patients' self-management web portal homepage



Appendix 3: Health status based on time in therapeutic (TTR) (for INR range 2-3.5) for the three groups. Figure 2B shows TTR values using the INR 2-3.5 in the three groups, 6 months before the intervention and in the 3 x 6-month periods after the intervention. Analysis of the three groups showed that the TTR values differed significantly over time (p=0.017). No significant differences were found in TTR between the groups (p=0.163) or between the groups over time (p=0.545).

Analysis of the two self-management groups showed significant differences in the TTR values between the four time periods (i.e. pre- and postintervention) (p=0.008). There were no significant differences in TTR between group 1 and 2 (p=0.721) or between the groups over time (p=0.825).

Equivalent health status for e-learning, group training self-management or usual care in oral anticoagulation patients: a parallel cohort design in the PORTALS Study

STROBE statement, checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract		
	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract – Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found – Page 2
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported – Page 3 (Introduction)
Objectives	3	State specific objectives, including any prespecified hypotheses – Page 4 (Introduction)
Methods		
Study design	4	Present key elements of study design early in the paper – Page 5/6 (Study design) + figure 1
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection – Page 5 (Study design) + reference 28
Participants	6	(*a*) *Cohort study*?Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up – Page 6 (Participants) + reference 28
		(*b*) *Cohort study*?For matched studies, give matching criteria and number of exposed and unexposed Participants were not matched + figure 1
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give

	Item No	Recommendation
		diagnostic criteria, if applicable – Page 8/9 (Outcome measures and determinants)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). – Page 8/9 (Outcome measures and determinants) Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias – Page 9 (Sample size and statistical methods)
Study size	10	Explain how the study size was arrived at – Page 9 (Sample size and statistical methods)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why – Page 8/9 (Outcome measures and determinants)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding – Page 9 (Sample size and statistical methods)
		(*b*) Describe any methods used to examine subgroups and interactions – Page 9 (Sample size and statistical methods)
		(*c*) Explain how missing data were addressed – Page 9 (Sample size and statistical methods)
		(*d*) *Cohort study*?If applicable, explain how loss to follow-up was addressed – Page 9 (Sample size and statistical methods)
		(*e*) Describe any sensitivity analyses Not applicable.
Results		
Participants	13*	(*a*) Report numbers of individuals at each stage of study?eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed – Page 9/10 (Results)
		(*b*) Give reasons for non-participation at each stage – Page 10/11 (Baseline characteristics of study participants)
		(*c*) Consider use of a flow diagram Figure 2.
Descriptive data	14*	(*a*)Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders – Page 10/11 (Baseline characteristics of study participants)

	Item No	Recommendation
		(*b*) Indicate number of participants with missing data for each variable of interest – Page 10/11 (Baseline characteristics of study participants) + Table 3
		(*c*) *Cohort study*?Summarise follow-up time (eg average and total amount) – Page 8/9 (Outcome measures and determinants)
Outcome data	15*	*Cohort study*?Report numbers of outcome events or summary measures over time – Page 12/13 (Usage of the platform)
Main results	16	(*a*) Report the numbers of individuals at each stage of the study?eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed – Page 9/10 (Results)
		(*b*) Give reasons for non-participation at each stage – Page 9/10 (Results)
		(*c*) Consider use of a flow diagram Figure 2.
Other analyses	17	Report other analyses done?eg analyses of subgroups and interactions, and sensitivity analyses Page 12 (Health status before and after intervention/Educational level and GSES)
Discussion		
Key results	18	Summarise key results with reference to study objectives – Page 13 (Discussion)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias – Page 13/14 (Strenghts and limitations)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence – Page 14/15 (Interpretation of findings)
Generalisability	21	Discuss the generalisability (external validity) of the study results – Page 16 (Interpretation of findings)
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based – Page 17 (Funding)

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross sectional studies.

The STROBE checklist is best used in conjunction with the explanation and elaboration article.[18-20] This article and separate versions of the checklist for cohort, case-control, and cross sectional studies are available at www.strobe-statement.org.