Effectiveness of Smartphone Applications vs Conventional Care in Warfarin Therapy: A Randomized Controlled Trial on the Time in the Therapeutic Range

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ABSTRACT

Objective: Warfarin is extensively used as an oral anticoagulant; however, its clinical application is complicated by a narrow therapeutic index. This investigation evaluated the efficacy of a drug reminder application versus traditional care in facilitating patients' maintenance of the therapeutic range, as well as in stabilizing the time in the therapeutic range (TTR).

Materials and Methods: This was a single-blind randomized controlled trial. Eligible participants were patients receiving warfarin therapy for at least 3 months and demonstrating at least two consecutive international normalized ratio (INR) values within the therapeutic range of 2 to 3 during the preceding 6 months. Patients in the intervention group were provided with a smartphone-based drug reminder application. All participant INRs were collected for 6 months. The outcome measures were TTR, INR, TTR of drug-drug interactions, and warfarin-related complications.

Results: Forty patients were recruited between January 2021 and August 2023. The mean TTR was 66.11%±9.8% for the intervention group and 67.31%±18.08% for the control group. With analysis of covariance, the results were slightly better in the intervention group, but the differences were not statistically significant (95%CI = -5.67 – 1.92, P-value = 0.323). For the 6-month INR monitoring, 6 out of 8 patients who could maintain the therapeutic INR range were in the intervention group. There were no statistically significant differences in warfarin-related complications between the two groups (20% vs 15%, RR 1.333, 95%CI = 0.3413 – 5.2086, P-value = 0.6790).

Conclusion: The drug reminder application likely improved the TTR, although without statistical significance. Further studies are needed to identify technology assistance in improving treatment outcomes.

Keywords: Warfarin; smartphone; application; patient compliance; anticoagulation (Siriraj Med J 2024; 76: 444-453)

INTRODUCTION

Warfarin is the most widely used oral anticoagulant for preventing thrombosis. The benefits of warfarin include preventing stroke in patients with prosthetic heart valves and atrial fibrillation, preventing venous thromboembolism, and preventing systemic thromboembolism.[1] Nevertheless, warfarin, known as a high-alert drug, has a narrow therapeutic index with individual variability in dose response

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affected by two genes, CYP2C9 (cytochrome P450 2C9) and VKORC1 (vitamin K epoxide reductase complex, subunit 1),[2,21] which results in bleeding complications.[3,4] Careful monitoring of the international normalized ratio (INR) is required to maximize its safety and efficacy. The optimal INR range is between 2.0 and 3.0.[5]

Apart from its narrow therapeutic index, warfarin is also subject to numerous interactions, especially with drugs that affect the cytochrome P450 system by CYP 2C9, 1A2, and 3A4 enzymes, as this pathway metabolizes warfarin.[20] These interactions can potentiate or inhibit the effects of warfarin, which may increase or decrease the INR.[20]

New oral anticoagulants, such as nonvitamin K antagonist oral anticoagulants (NOACs), are safer than warfarin and are commonly used in developed countries. Because of its cost-effectiveness, warfarin is still prescribed in other countries. Furthermore, the new oral anticoagulants have some limitations. The lack of evidence supporting the efficacy of NOACs for preventing stroke in patients with prosthetic heart valves,[6] the limitations of laboratory monitoring of their efficacy,[7] and the much greater price of NOACs compared with warfarin are reasons why warfarin is still included in Thailand's National List of Essential Medicines.[8]

According to data on warfarin use at Siriraj Hospital collected in 2019, there are still problems with drug use, which causes ineffectiveness of the INR. The problems included warfarin nonadherence (11.7%), drug–drug interactions (8.7%), minor bleeding (6.4%), food–drug interactions (2.9%), disease–drug interactions (1%), smoking–drug interactions (1%), and herb/supplement–drug interactions (0.5%). Therefore, the most common problems associated with using warfarin are nonadherence and drug–drug interactions.

"Nonadherence" is defined as the failure to follow a prescribed therapeutic regimen. It is divided into two types: intentional and unintentional medication nonadherence.[14] In the previous study, overadherence (>10% extra doses) and underadherence (>20% missed doses) with warfarin therapy had clinically significant levels of nonadherence.[22] Recent research on nonadherence to warfarin revealed levels of 41.8% among patients with non-valvular atrial fibrillation at Samsung Medical Center in Korea[9] and 16% among patients prescribed warfarin in a midwestern urban hospital in the USA.[10] Other studies on drug–drug interactions have shown that acetaminophen[2] and antibiotics,[11] such as fluoroquinolones and macrolides, increase the effects of warfarin, causing INR prolongation and encouraging warfarin nonadherence. The factors affecting nonadherence to warfarin drug use include a lower Short Form (SF)-36 mental component score, and impaired cognitive function (≤19 points) on the Cognitive Capacity Screening Examination (CCSE), education beyond high school.[12] Trachtenberg et al.[23] explained that higher education levels might relate to more independent decision making or has been guided by other settings to diminished trust in physicians relative to less educated subjects. Additionally, disabled patients aged over 55 years tend to have worse adherence (OR 1.8 [1.1–3.1])[12] than younger disabled patients.

Recently, several studies have examined interventions for improving warfarin adherence. They include a warfarin-medication therapy-adherence clinic protocol (a retrospective cohort study in Malaysia),[13] a repeated-education and follow-up plan (a prospective randomized trial in Croatia),[14] telephone follow-up interventions (a randomized controlled trial in Thailand),[15] and a smartphone application (a prospective case series in China).[16] The outcomes of these investigations favored the intervention groups in terms of increasing the time in the therapeutic range (TTR).

At Siriraj Hospital, a warfarin drug advice brochure is given to patients. Nevertheless, this approach is inadequate for resolving the nonadherence problem, as revealed by analyzing individual INR variabilities. If patients can stabilize their INR, the adverse effects arising from the use of warfarin will be averted. The most common cause of out-of-range INR is nonadherence to drug use. In the present technological period, we are interested in using an application to help patients maintain their optimal INR. We gathered data for research on the variability of INR levels from the Warfarin Clinic at Siriraj Hospital. The primary objective of the present study was to achieve a stable TTR by using a smartphone-based application that helps decrease nonadherence. The secondary objectives were TTR of drug-drug interactions and warfarin-related complications.

MATERIALS AND METHODS

Study design

This single-blinded, randomized, controlled trial was approved by the Siriraj Institutional Review Board, Faculty of Medicine Siriraj Hospital, Mahidol University (SI 501/2020) and was registered in the Thai Clinical Trials Registry (TCTR20200925001). The study was conducted at the Warfarin Clinic at Siriraj Hospital, between January 2021 and August 2023. Participants who used warfarin were recruited. All participants provided informed consent before commencing the study. A flowchart of the study according to the Consolidated Standards of Reporting Trials (CONSORT) is shown in the Fig. Single-blinded

design in this study refers to the research assistant who was blinded to the randomization.

Participants and Randomization

The inclusion criteria were an age of at least 18 years; having undergone warfarin therapy for ≥3 months with two or more consecutive INR values in the range of 2 to 3 within 6 months before recruitment; an older patient (age ≥60) with a Thai Mental State Examination score ≥23 or a dementia patient with a caregiver; access to a smartphone with internet access; and proficiency in Thai. The exclusion criteria were patients with severe medical conditions that might affect their life, such as malignancy, end-stage renal disease, or severe hepatic impairment.

The criteria for the withdrawal of participants from the study were as follows: (1) nonadherence to protocol, i.e., voluntary withdrawal at any time due to an inability to comply with the study requirements, an inability to check INR levels monthly, or some other reason (e.g., feeling uncomfortable with the application use); (2) loss to follow-up or ; or (3) any contraindication to warfarin during the study period after the randomization (e.g., central nervous system hemorrhage, therapeutic procedure with the potential for significant bleeding)

All participants were screened to determine their eligibility based on inclusion and exclusion criteria by a research assistant who was blinded to the randomization. A randomization was done after the enrollment. The random allocation sequence was created using a computer generated random number table.

Outcomes Measures

The demographic data included sex, age (<60 years old, >60 years old), body mass index (<18.5 kg/m^2, 18.5–22.9 kg/m^2, 23.0–24.9 kg/m^2, 25.0–29.9 kg/m^2, >30 kg/m^2), indications, level of education, functional capacity (<4 metabolic equivalents, >4 metabolic equivalents), duration of previous warfarin therapy (<1 year, 1–3 years, 3–5 years, >5 years), history of smoking and alcohol consumption, comorbidities, and laboratory data (including estimated glomerular filtration rate [eGFR], prestudy TTR, total bilirubin, direct bilirubin, serum glutamic-oxaloacetic transaminase [SGOT], and serum glutamic pyruvic transaminase [SGPT]).

The primary outcome measure was the time in

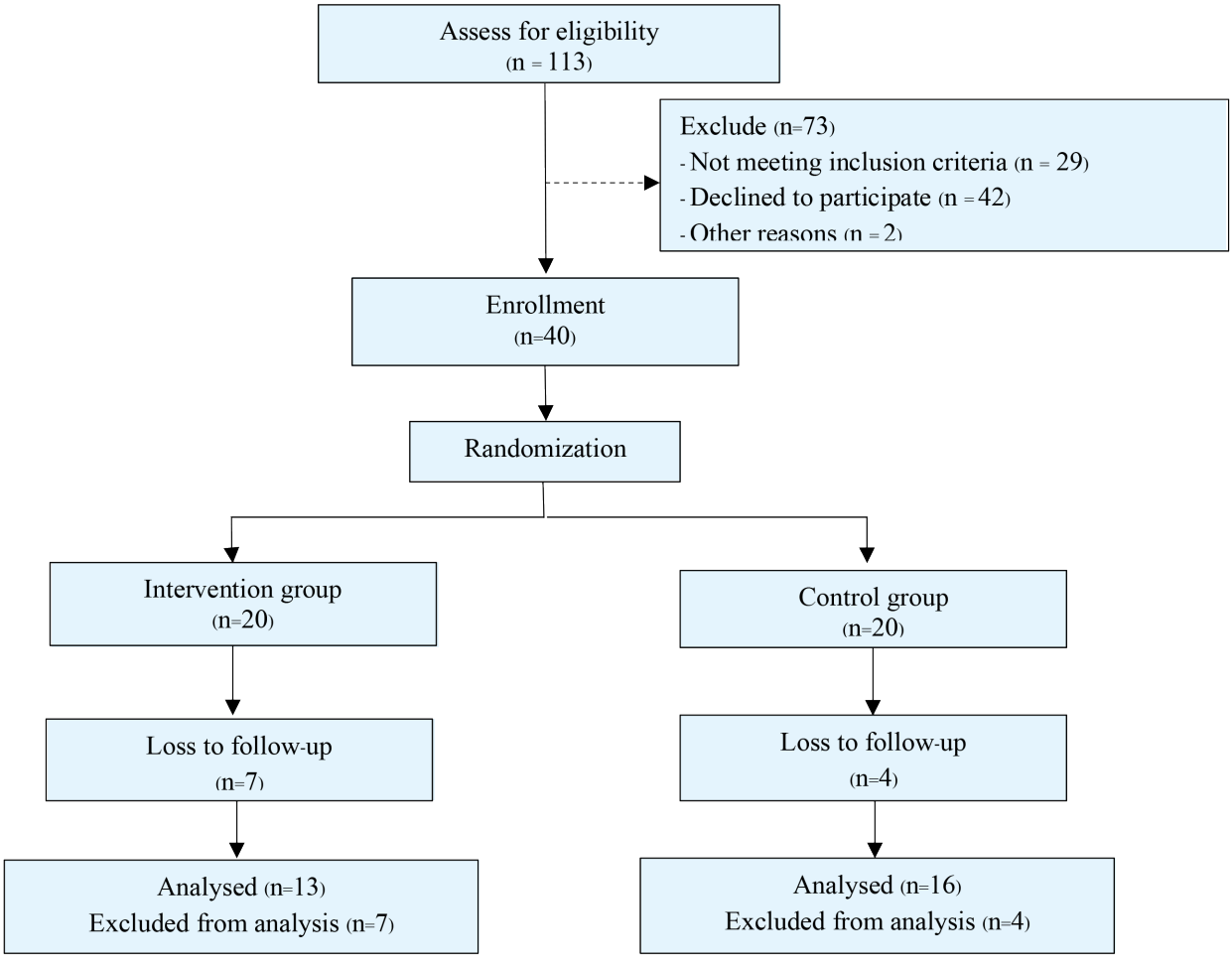

Fig. CONSORT flow diagram of participant enrollment and study progression.

therapeutic range (TTR), a quality measure commonly used for anticoagulation therapy with warfarin.[17] The TTR represents the percentage of time when the INR is in the 2.0 to 3.0 target range across a given period.[18] In the present study, the TTR was calculated as the number of times that the INR was within the therapeutic range divided by the total number of times that the INR was evaluated during the observation period. We defined a "good TTR" as a level of 60% or more.[19] Apart from the TTR, the 6 monthly INR follow-up data points were monitored and categorized into three ranges: therapeutic, subtherapeutic, and supratherapeutic. The participants were assigned to the therapeutic-range group if all of their follow-up data were in the range of 2.0–3.0, the subtherapeutic-range group if at least one of the follow-up INR values was below 2.0, and the supratherapeutic-range group if at least one of the follow-up INR values was above 3.0. The secondary outcomes were the relationship between drug–drug interactions and the TTR, and the occurrence of warfarin-related complications.

Interventions

Participants were randomly assigned to either an intervention group or a control group by computer randomization. Those in the intervention group received standard treatment and instructions on utilizing two smartphone applications, while those in the control group were limited to standard treatment alone. Standard therapy, provided by pharmacists at Siriraj Hospital's Warfarin Clinic, included conventional pharmacological management, direct patient education regarding warfarin, the distribution of information brochures, and a calendar with significant dates marked.

The intervention involved the "Drug Diary" application and the "LINE" application. The Drug Diary application is designed to enhance medication adherence by alerting patients about their medication schedules and dosages. The application is accessible at no cost on either the Android or the IOS platform. Intervention group participants received assistance in downloading the application, along with comprehensive training for both patients and their caregivers on its use. The LINE application enabled the intervention group participants to submit images and details of nonwarfarin medications to the research team for assessment of potential interactions with warfarin. Group assignment, baseline demographic and clinical data were collected for all participants by a researcher, who was not engaged in the outcome assessment. Follow-up assessments, including monthly International Normalized Ratio (INR) evaluations for six months, were conducted by Warfarin Clinic pharmacists. These assessments also included a review of any other medications taken in the preceding month and the recording of any adverse effects related to warfarin, such as abnormal bleeding or hospitalization. For those in the intervention group, adherence to the app was gauged by comparing the warfarin pill count logged in the app against the actual pill count derived from the prescribed amount minus the quantity remaining at follow-up. Participants showing a discrepancy of 10% or more were excluded from the study.

Statistical analysis

The sample size for this investigation was determined using nQuery Advisor software. The calculation drew upon baseline TTR data sourced from the Warfarin Clinic at Siriraj Hospital, which was established at 48.5%. The TTR was calculated by Rosendaal method.[25] The study posited that the intervention would enhance TTR by a minimum of 35% from the baseline, achieving a target TTR of 65.5%. With a standard deviation of 18.9, an alpha level of 0.05, and a power of 80%, the required sample size was established at 20 participants per group. Anticipating a 20% dropout rate, the adjusted sample size was set at 25 individuals per group.

Statistical analyses were conducted utilizing IBM SPSS Statistics, version 28 (IBM Corp, Armonk, NY, USA).[26] Participant demographics and clinical attributes were delineated using descriptive statistics. The chi-square test was used to compare categorical variables such as sex, age, body mass index, clinical indications, educational level, functional capacity, duration of prior warfarin therapy, smoking status, alcohol use, and comorbid conditions between groups, with results presented as percentages. Continuous variables, including eGFR, prestudy TTR were analyzed using the independent t test and are expressed as means with standard deviations (SDs). Other continuous variables, such as total bilirubin, direct bilirubin, SGOT, and SGPT, were analyzed by using Mann-Whitney U test. The primary outcome measures, encompassing pre- and posttreatment TTR, were also compared between groups using the independent t test and are summarized as means with SDs. Analysis of covariance (ANCOVA) was utilized to assess the mean difference in TTR between groups, accounting for baseline measurements as covariates. Z-test statistic was applied to evaluate six-month follow-up data, TTR related to drug–drug interactions, and complications associated with warfarin, with findings reported as percentages. The threshold for statistical significance was set at an alpha level of 0.05.

RESULTS

Study Participants

This study included 40 patients receiving oral anticoagulant therapy, who were equally randomized into intervention and control groups. Of these, 11 patients were withdrawn due to loss to follow-up (7 from the intervention group and 4 from the control group).

Table 1 presents the demographic characteristics of the participants before the study commenced. The analysis revealed no statistically significant differences between the groups ($p > 0.05$), except for their age distributions. The intervention group had a greater proportion of participants aged 60 years or younger, while the control group predominantly consisted of those older than 60 years. To mitigate the potential confounding effect of age-related cognitive impairment, our inclusion criteria were stringent: only individuals older than 60 years with a Thai Mental State Examination score exceeding 23 points or those with dementia but under caregiver supervision were enrolled, ensuring adherence to prescribed medication regimens. As indicated in Table 1, most participants were female (67.5%), with 65% of the intervention group and 35% of the control group being 60 years old or younger. Valvular heart disease was the most prevalent indication for warfarin therapy and was observed in 95% of patients. The educational background of most participants was elementary level (58.3%), and the majority had been on warfarin for 3 to 5 years (65%).

The baseline characteristics, including age, sex, body mass index, educational attainment, indications for warfarin therapy, duration of treatment, functional capacity, smoking and alcohol use history, comorbidities, and laboratory parameters such as eGFR, prestudy TTR, total bilirubin, direct bilirubin, SGOT, and SGPT, were similar across both groups.

Outcomes of anticoagulation therapy

Table 2 delineates the laboratory outcomes within and between the groups involved in the study. Initially, the TTR prior to the study exhibited no significant difference between the groups. To ascertain more precise measurements, an ANCOVA was employed, taking the pretreatment TTR as a covariate to evaluate the differences in TTR before and after treatment across the groups. The findings indicated a marginally improved TTR in the intervention group compared to the control group, although this difference did not reach statistical significance.

Over the six-month monitoring period, the intervention group demonstrated superior outcomes, with 75% (6 out of 8) of its participants successfully maintaining their INR within the therapeutic range. There was no significant difference in the TTR related to drug-drug interactions between the groups.

Table 3 presents the incidence of warfarin-related complications encountered throughout the study. A solitary minor bleeding event was reported, involving a total of 7 participants (4 from the intervention group and 3 from the control group).

DISCUSSION

Despite the prevalence of warfarin as a primary oral anticoagulant for thrombosis prevention,[1] its narrow therapeutic index poses a significant risk for bleeding complications.[2–4] Meticulous monitoring of the INR is essential to mitigate such adverse events.[5] Nonadherence emerges as a pivotal challenge in maintaining the INR within the therapeutic window.[9,10] Given the limited dosage range of these medications, numerous studies have explored various interventions to sustain the INR within the desired therapeutic range.[13–16] The advent of smartphones has catalyzed the development of medication reminder applications, among which Drug Diary stands out for its user-friendly interface and timely notifications in Thai, aimed at enhancing medication adherence.[27]

The present investigation represents a pioneering effort to examine the efficacy of a drug reminder application in managing warfarin therapy through a randomized controlled trial. Participants utilizing the application exhibited a tendency toward improved INR optimization and a marginal enhancement in their TTR compared to those receiving standard care, although the difference did not reach statistical significance.

Previous studies have assessed the impact of various interventions on the TTR. These interventions range from repeated education and follow-up sessions[13–14] to telephone follow-ups that extend the duration of INR values within the therapeutic range.[15] Furthermore, smartphone applications designed to remind patients about their medication schedules and INR testing have been shown to enhance TTR in groups with high adherence.[16] In line with these findings, our study also noted a modest improvement in the median TTR among participants in the intervention group, consistent with the outcomes reported in the aforementioned studies.[16]

The Drug Diary reminder application offered a substantial benefit beyond merely ensuring timely medication intake: it facilitated sustained INR levels within the therapeutic range by bolstering daily medication adherence. Furthermore, this study incorporated the use of the LINE application, which is increasing in popularity among smartphone users, to monitor concomitant medications

TABLE 1. Baseline demographic and clinical characteristics of participants.

Variables	Total (N=40)	Intervention (N=20)	Control (N=20)	P-value
Demographic data	-	-	-	-
Gender	-	-	-	0.501[a]
Female	27 (67.5%)	12 (60%)	15 (75%)	-
Male	13 (32.5%)	8 (40%)	5 (25%)	-
Age, years				0.010[a]
≤ 60 years	17 (42.5%)	13 (65%)	4 (20%)	-
> 60 years	23 (57.5%)	7 (35%)	16 (80%)	-
BMI	-	-	-	0.697[a]
< 18.5	0 (0%)	0 (0%)	0 (0%)	-
18.5 – 22.9	16 (40%)	8 (40%)	8 (40%)	-
23.0 – 24.9	7 (17.5%)	5 (25%)	2 (10%)	-
25.0 – 29.9	15 (37.5%)	6 (30%)	9 (45%)	-
> 30	2 (5%)	1 (5%)	1 (5%)	-
Indication(s)	-	-	-	-
Mechanical prosthetic valve	0 (0%)	0 (0%)	0 (0%)	-
Tissue heart valves	3 (7.5%)	1 (5%)	2 (10%)	1.000[a]
Valvular heart disease	38 (95%)	19 (95%)	19 (95%)	1.000[a]
Atrial fibrillation	15 (37.5%)	8 (40%)	7 (35%)	1.000[a]
Deep vein thrombosis	0 (0%)	0 (0%)	0 (0%)	-
Pulmonary embolism	0 (0%)	0 (0%)	0 (0%)	-
Education	-	-	-	0.192[a]
No formal education	2 (5.6%)	1 (5.6%)	1 (5.6%)	-
Elementary school	21 (58.3%)	7 (38.9%)	14 (77.8%)	-
High school	6 (16.7%)	5 (27.8%)	1 (5.6%)	-
College	3 (8.3%)	2 (11.1%)	1 (5.6%)	-
University	4 (11.1%)	3 (16.7%)	1 (5.6%)	-
Functional capacity	-	-	-	1.000[a]
< 4 MET	1 (7.7%)	0 (0%)	1 (12.5%)	-
≥ 4 MET	12 (92.3%)	5 (100%)	7 (87.5%)	-
Length of previous warfarin therapy	-	-	-	0.757[a]
< 1 year	3 (7.5%)	1 (5%)	2 (10%)	-
1-3 years	5 (12.5%)	3 (15%)	2 (10%)	-
3-5 years	6 (15%)	4 (20%)	2 (10%)	-
More than 5 years	26 (65%)	12 (60%)	14 (70%)	-
Smoking	-	-	-	0.605[a]
No	35 (89.7%)	17 (85%)	18 (94.7%)	-
Yes	4 (10.3%)	3 (15%)	1 (5.3%)	-

TABLE 1. Baseline demographic and clinical characteristics of participants. (Continue)

Variables	Total (N=40)	Intervention (N=20)	Control (N=20)	P-value
Alcohol consumption	-	-	-	1.000[a]
No	38 (95%)	19 (95%)	19 (95%)	-
Yes	2 (5%)	1 (5%)	1 (5%)	-
Comorbidities	-	-	-	-
Cardiovascular system	-	-	-	-
HT	21 (52.5%)	8 (40%)	13 (65%)	0.205[a]
IHD/ MI	3 (7.5%)	1 (5%)	2 (10%)	1.000[a]
AF	16 (40%)	9 (45%)	7 (35%)	0.748[a]
VHD	36 (90%)	17 (85%)	19 (95%)	0.605[a]
CHF	1 (2.5%)	1 (5%)	0 (0%)	1.000[a]
Respiratory system	-	-	-	-
Asthma	2 (5%)	0 (0%)	2 (10%)	0.487[a]
Endocrine system	-	-	-	-
DLP	15 (37.5%)	7 (35%)	8 (40%)	1.000[a]
DM	7 (17.5%)	4 (20%)	3 (15%)	1.000[a]
Neurological system	-	-	-	-
CVA	6 (15%)	5 (25%)	1 (5%)	0.182[a]
Hemiparesis	2 (5%)	1 (5%)	1 (5%)	1.000[a]
Renal system	-	-	-	-
CKD	10 (25%)	5 (25%)	5 (25%)	1.000[a]
Hepato-biliary system	-	-	-	-
Cirrhosis	1 (2.5%)	0 (0%)	1 (5%)	1.000[a]
Laboratory data	-	-	-	-
eGFR; mean ± SD	86.85 ± 22.23	94.96 ± 18.07	66.58 ± 19.85	0.024[a]
Pre study TTR; mean ± SD	66.92 ± 16.09	65.06 ± 12.74	68.79 ± 19.02	0.470[b]
Total bilirubin; median (min, max)	0.82(0.32, 1.52)	0.47(0.32, 1.52)	0.87(0.82, 0.92)	0.800[c]
Direct bilirubin; median (min, max)	0.25(0.13, 0.85)	0.22(0.13, 0.85)	0.325(0.25, 0.40)	0.800[c]
SGOT; median (min, max)	32(14, 59)	23(14, 59)	38(36, 58)	0.250[c]
SGPT; median (min, max)	24(9, 56)	19(9, 56)	31(26, 48)	0.250[c]

[a] chi-square test
[b] t- test
[c] Mann-Whitney U test

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CHF, congestive heart failure; CKD, chronic kidney disease; CVA, cardiovascular accident; DLP, dyslipidemia; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HT, hypertension; IHD, ischemic heart disease; MET, metabolic equivalents; MI, myocardial infarction; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; TTR, time in therapeutic range; VHD, valvular heart disease

TABLE 2. Outcomes of anticoagulation therapy: therapeutic range and time in therapeutic range.

Variables	Total	Intervention	Control	Δ Mean difference between groups (95% CI)	Relative risk (RR)	P-value
Primary outcome						
Pre study TTR (%)	66.92 ± 16.09	65.06 ± 12.74	68.79 ± 19.02	3.74 (-6.63, 14.10)[a]	-	0.470[a]
Post study TTR (%)	66.70 ± 14.39	66.11 ± 9.85	67.31 ± 18.08	1.21 (-8.12, 10.53)[a]	-	0.795[a]
Δ Mean difference between post TTR and pre TTR (%)	-	67.65 ± 1.32	65.77 ± 1.32	- 1.87 (- 5.67, 1.92)[b]	-	0.323[b]
INR values in range	8 (20%)	6 (30%)	2 (10%)	(0.686, 13.119)[c]	3.000	0.144[c]
Out of range INR values	-	-	-	-	-	-
Subtherapeutic	18 (45%)	4 (20%)	14 (70%)	(0.114, 0.719)[c]	0.286	0.008[c]
Supratherapeutic	14 (35%)	10 (50%)	4 (20%)	(0.9385, 6.661)[c]	2.500	0.067[c]
Secondary outcome	-	-	-	-	-	-
TTR of drug-drug interaction	-	-	-	-	-	-
With drug-drug interaction (%)	-	65.80 ± 1.56	64.70 ± 1.713	- 1.10 (-5.97, 3.77)[b]		0.641[b]
Without drug-drug interaction (%)		70.29 ± 2.35	66.94 ± 2.10	- 3.35 (-10.10, 3.38)[b]		0.305[b]

[a] Between-group p value was calculated by paired t tests
[b] Mean difference between groups and p value was calculated by analysis of covariance with pretest as covariate.
[c] calculated by z statistic
Abbreviations: INR, international normalized ratio; TTR, time in therapeutic range

TABLE 3. Incidence of warfarin-related complications during the study period.

Variables	Total	Intervention	Control	95%CI	RR	P-value
Thromboembolic events	0 (0%)	0 (0%)	0 (0%)	-	-	-
Bleeding events	-	-	-	-	-	-
Major bleeding	0 (0%)	0 (0%)	0 (0%)	-	-	-
Minor bleeding	7 (17.5%)	4 (20%)	3 (15%)	(0.341, 5.209)[a]	1.333	0.679[a]
Warfarin-related hospital admission	0 (0%)	0 (0%)	0 (0%)			-

[a] calculated by z statistic

and educate patients about potential drug interactions with warfarin. However, the participants in the intervention group who loss to follow up has nearly been doubled compared with the control group. Nonadherence can occur in randomized clinical trial due to unfollowing the randomly assigned treatment protocol. The causes of nonadherence may include not taking trial medications, crossing over to the other intervention being studied, assessing treatment outside of trial or not being able to complete the assigned therapy by the clinician.[24] Therefore, the participants with the application who loss to follow up may be considered as one type of nonadherence.

Interestingly, participants in the intervention group reported a greater incidence of drug–drug interactions than did those in the control group. Nonetheless, the frequency of warfarin-related complications, such as minor bleeding events, did not differ significantly between the groups. This outcome may be attributed to the proactive management of interacting medications facilitated by the LINE application, potentially preventing further complications. We hypothesize that the combined use of the Drug Diary and LINE applications enhances medication adherence and reduces adverse events stemming from drug interactions.

In addition to the use of the two smartphone-based applications, several other elements may have influenced medication adherence. In a study by Li et al,[16] logistic regression analysis revealed that having more than 6 years of formal education was the only predictor of good compliance. In the present investigation, we found that the patients in the intervention group tended to have greater educational attainment than did those in the control group. This difference in educational level may have contributed to the intervention group's tendency towards comparatively better INR optimization and TTR. Furthermore, being aged 60 years or younger could also contribute to better adherence, as evidenced by the majority of younger participants in the intervention group. Despite these age-related trends, the potential confounding effect of older age was mitigated through the Thai Mental State Examination assessment and by ensuring that caregivers were responsible for medication management in patients with dementia. Consequently, the observed age disparity is unlikely to have significantly impacted medication compliance within this study. These findings suggest that the use of information technology may be more readily accepted by individuals with certain demographic profiles, thereby influencing adherence.

Limitations

This study has several limitations. First, the small sample size posed a limitation. Despite efforts to recruit all eligible candidates, 73 patients were ultimately excluded, rendering our sample size modest relative to that of other studies. Furthermore, the participants were drawn exclusively from the Warfarin Clinic at Siriraj Hospital, potentially limiting the generalizability of our findings and introducing selection bias. Also, in order to avoid selection bias, allocation concealment should be performed. Additionally, some patients did not understand that the study required monthly INR evaluations. This led to their withdrawal from the study, thereby exacerbating statistical bias. Last, the study's definition of the therapeutic INR range as 2.00–3.00 may not be applicable to the broader patient population, further limiting the generalizability of our results.

CONCLUSION

The use of the Drug Diary reminder application alongside the LINE application was observed to potentially enhance TTR and maintain INR within the therapeutic spectrum. However, these improvements did not achieve statistical significance. To substantiate the benefits of these digital interventions over conventional anticoagulation management, expanded research involving a larger cohort and multicenter trials is recommended.

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Conflict of Interest

Authors declare no conflict of interest for this article.

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