The Impact of Using Mobile Applications on Health Outcomes in Patient Self-Management of Oral Anticoagulation Therapy

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Abstract

Background

Between one and two percent of the population of the developed countries are currently treated with oral anticoagulation therapy. The transition of all or part of the responsibility for therapy management to the patient is an appropriate strategy to respond increasing demand for oral anticoagulation therapy. The main objective of this original study was to investigate the impact of using mobile applications on health outcomes in patient self-management of oral anticoagulation therapy.

Methods

The papers reviewed in this study had two key characteristics: firstly, they were written in English, and secondly, they used mobile application in oral anticoagulation therapy. An Android mobile application called XrinA was developed to provide warfarin patient self-management. The study was conducted following a Before-After study design. In the Before and After periods, patients were treated as usual and by using the developed application, respectively.

Results

In the Before period, the mean percentage of International Normalized Ratios (INRs) within the therapeutic range and Time in Therapeutic Range (TTR) of patients was 31.63% and 34.4%, respectively. In the After period, the mean percentage of INRs within the therapeutic range and TTR of patients was 41.41% and 49.97%, respectively. In the After period, the mean INRs within the therapeutic range and the mean TTR increased by 9.78% and 15.57%, respectively.

Conclusions

Overall, the use of mHealth applications improved outcomes in patient self-management of oral anticoagulation therapy in terms of the percentage of INRs within the therapeutic range and TTR.

Background

Different types of thrombosis and thromboembolic events can be usually prevented and treated using anticoagulants [1]. As long as such therapy is required for outpatients, oral anticoagulants, that do not require hospitalization and are more compatible with patients’ daily lives, are utilized [2-4].

Oral anticoagulants include both the Vitamin K Antagonists (VKAs) and newer drugs known as the Novel Oral Anticoagulants (NOACs) [5]. Despite the advent of NOACs, there is limited information on their use in patients with renal dysfunction, obese patients, pediatric population, and pregnant women [5], and there is no antidote for many of these drugs [6]. Moreover, they cost much more than VKAs [5]. Therefore, VKAs, especially warfarin, line up as the first-choice treatment for a large group of patients [6]. Currently, between one and two percent of the population of the developed countries are estimated to receive oral anticoagulants, especially warfarin, on a regular basis [7].

It should be pointed out that the impact of VKAs depends on receiving appropriate doses [5]. To ensure the effective course of VKA therapy, the Prothrombin Time (PT) test should be performed frequently and at regular intervals in order to determine the extent to which the results lie within the therapeutic range, which is regarded as an important indicator of therapy effectiveness [8-10]. The percentage of Time in Therapeutic Range (TTR) is a direct measure of the quality of VKA therapy management that can be calculated using various methods. The linear interpolation described by Rosendaal is mostly effective in calculating the percentage of TTR [11, 12]. TTR refers to the ratio of the number of total days between the two tests in which the patient's International Normalized Ratio (INR) lies within the therapeutic range [13, 14].

Currently, the growing trend of cardiovascular disease (CVD) and the increase in the population taking oral anticoagulants in the world [15, 16] as well as the lack of development of facilities commensurate with this increased requirement give rise to more increase in demand than in supply. For instance, if all patients in the UK wanted to attend anticoagulation clinics (ACs) in hospitals, the current number of clinics would have to increase five to tenfold [17]. Therefore, developing methods with the capability of continuous monitoring of the patient's conditions at home, work, travel, or in any circumstance at a lower cost and with the shortest time will be of paramount importance.

Studies have shown that the utilization of electronic health (eHealth) applications in patient self-management (PSM) has been effective in chronic diseases [18, 19]. These applications serve as a reminder to improve medication adherence and monitor, assist, and inform patients as well [18]. Utilizing these applications by minimizing or even eliminating the need for clinic visits for routine treatment of some common complications and by facilitating self-management can contribute to the patient's adherence to therapy and increasing the duration of time in which the patient remains within the target therapeutic range and the percentage of TTR [20].

The results from a systematic review [21] on investigating the characteristics of mobile applications used in patient self-management of VKAs therapy were as follows. Some applications were developed commercially and some were freely accessible to users. Some required username and password to login and some could run without them. Moreover, some applications used cryptography to tighten the security of medical information exchange and some were developed in a bilingual manner. Most of the applications had training modules that were implemented as frequently asked questions (FAQs) in some of them, and some had training videos. Besides, some applications provided the necessary information regarding vitamin K in foods, training on anticoagulation therapies, and safety tips. Drug interactions as well as food-drug interactions were also presented in some applications. Simple and specific safety tips associated with warfarin treatment, such as preventing injury and when to contact a doctor, were also given in some applications. Some applications possessed the capability for utilizing a smartphone camera which made it possible to capture pictures of a bleeding or bruised area and store it to present to a physician in clinics.

Some applications ran in stand-alone mood and some could run using the network connection. Furthermore, in some cases, these applications could be integrated with other applications in medical centers. Some applications were accessible on the Internet, and some could also be connected to the point-of-care testing (POCT) equipment.

Until 2016, SMS was the most common type of mobile technology application in chronic diseases (about 40%). Currently, some commercial apps have been applied to various fields, including medication reminders and those determining vitamin K content of foods. Some apps were also utilized as visit time reminders. Each application was developed to run on the web, desktop, Android, or iOS environments and could run on iPod, palmtop (mobile, tablet), laptop, or personal computer (PC) platforms as well. Some applications, in addition to possessing the capability of being installed on a palmtop platform, had a web page provided to the physician for the purpose of reporting.

Application users included patients, physicians, and the care team. Some applications also possessed the capability to report INR results in a list or graph and to determine the duration of time in which the patients' INRs are within the therapeutic range. In these studies, the duration of application usage for treatment varied from six weeks to five years.

Concerning the user interface (UI), some applications were multimedia and some were textual. Besides, the UI of some apps was designed in a way that to be easy to use for the elderly; for instance, they had large keys and large fonts, and some of them possessed the capability to change the font, size, and color (text and background) as well.

In some applications, there was a possibility of setting up communication between the care provider and other trusted people such as family and friends. Sending messages to the physician to inform him/her of the duration of bleeding, time, pictures captured, and explanations were also feasible even after seeing the physician for an appointment. Moreover, some apps had the capability of sending SMS or e-mail, and in some other mobile applications, the patient could talk to the physician as well.

Furthermore, some applications had the Computerized Decision Support System (CDSS). In some apps, a calculator was embedded to calculate the risk of stroke and bleeding. Among the automated capabilities available in some apps, there was the possibility of automatic contact with patients as well as the predictability of the appropriate dosage and upcoming testing date.

Moreover, the following app samples used for oral anticoagulation therapy were presented based on a systematic review [21]. The CSO/AC application was developed as an expert anticoagulation system in Denmark. In this system, there is a possibility to establish communication between the patient and the health care team via the Internet. It possesses the capability to notify the patient by sending out alerts to immediately call the clinic, provided that the INR value is less than 1.5 or higher than 5. On average, the use of this application increased the number of INRs within the therapeutic range and TTR values by 12% and 7%, respectively. The SintromacWeb application made by Grifols was utilized for oral anticoagulation therapy telecontrol via the Internet in Spain. In this application, there is a possibility to set up an online communication between the patient and the physician. The utilization of this application gave rise to a 12.6% increase in TTR values as well as a reduction in the incidence of thrombotic events and bleeding. The AuriculA application was implemented in Sweden. Using the built-in algorithm, this application proposed the dosage and upcoming testing date for the INRs within a range of 2.0 – 3.0, which led to a 7% increase in the number of TTRs.

The results of a systematic review [22] regarding INR showed that patient self-management using eHealth applications did not reduce the number of INRs within the therapeutic range in any of the reviewed studies; therefore, it was recommended to replace the conventional methods with this method based on this index.

Moreover, in most studies of systematic review [22], the increase in the percentage of TTR was more than 5% as compared to the previous method, indicating that patient self-management of oral anticoagulation therapy using applications can be considered as an appropriate alternative to conventional methods.

Therefore, given the growing trend of using information technology (IT) in various fields of health as well as the lack of studies on the impact of using mobile health (mHealth) in oral anticoagulation therapy in developing countries, the current study was designed. The main objective of this original study was to investigate the impact of using mobile applications on health outcomes (the number of results of the INR within the therapeutic range and TTR) in patient self-management of oral anticoagulation therapies. However, in this study, warfarin was considered the oral anticoagulant of choice, not novel oral anticoagulants (NOACs).

Methods

Data Gathering Process

The reviewed papers in the study was conducted based on PRISMA protocol. The related checklist is presented in Appendix 1. Articles had two key characteristics: firstly, they were written in English, and secondly, they were utilized applications in oral anticoagulation therapy. The Cochrane, EMBASE, and PubMed databases were searched for all the papers that met the two above-mentioned criteria, without any restriction on the start date, until May 14, 2017. Articles searched via Google Scholar were then added to the study. The electronic search strategy was made up of MeSH and non-MeSH keywords as well as an appropriate combination of them, which are listed in Appendix 2.

During the paper selection process, studies that did not focus on the patient (for instance, studies focused on the care team) as well as papers that did not compare *management with application* with *management without application* in terms of health outcomes, and those papers that did not provide any explanations regarding applications were excluded from the study. Eventually, relevant and valid texts on the characteristics of mobile applications with the capabilities of medication reminders, visit time reminder, the feasibility of setting up communication between the patient and the physician, and the possibility of calculating warfarin dosage were studied. The different stages of filtering the articles have been shown in Appendix 3.

The current status of the warfarin prescription management process in the country was then analyzed through consulting a three-member research group consisting of a professor of the Department of Health

Information Management and Technology of the School of Paramedical Sciences as well as a cardiologist and a pharmacist of the selected hospitals.

The Mobile Application Development Process

The demands of application users were identified based on valid texts and experts' opinions. According to the relevant studies, the operating model of the mobile application for warfarin patient self-management (PSM) was developed, requirements for the mobile application were extracted, and use case diagrams as well as activity diagrams were drawn. Then, the structural model of the application was developed by extracting classes and drawing Class-Responsibility-Collaboration (CRC) models as well as the Entity Relationship Diagram (ERD). The behavioral model of the application was then developed by analyzing the system behavior and drawing the Sequence Diagram. After the conceptual model of the application was developed, the application platform and programming language were determined. Eventually, an Android mobile application called XrinA was developed for the purpose of warfarin PSM.

The application architecture was designed as a Client-Server model. The application consists of two running parts, including the server part running on the server and the client part running on physicians' and patients' phones. The task of the server part is to manage schedules and send reminders to the patient based on the physician's prescription. Besides, provided that no appropriate feedback is received from the patient about the prescription given, the server part will send out required alerts to the physician. The server part of the application was designed in the Microsoft Visual Studio 2015 and C# language. The client part, which is a mobile application, was designed in the Android Studio 3 and Java language. The server operating system, the Microsoft Windows Server 2016, and the operating system for clients (i.e., mobile phones) are based on Android. The application can be installed on mobile phones with the Android operating system and Android version 4.2.1 and above. The Microsoft SQL Server 2014 was used to manage the data. Data included patients' information, schedules associated with each patient, patients' test results, and the prescriptions given to each patient. The communication between clients and servers was also set up via the Internet and based on the Internet Protocol (IP) of each mobile phone and server. In order to use this application, it is a necessity that users' mobile phones should be always connected to the Internet and the application should be running (i.e., the users do not log out of the application through the “exit” menu). After coding, the application was tested and then was implemented.

To troubleshoot the application described, the three-member research group mentioned earlier was provided with the total application process flow and its content. The points of view of each of the mentioned individuals were adopted before and during the application development and then taken into account as well. The application was piloted for two weeks and then finalized.

Evaluation

Application users included physicians and patients; therefore, an attempt was made to select them. Among several hospitals and one clinic, the same clinic and a physician who met the inclusion criteria entered the study. Patients referred to the clinic were also selected through purposeful sampling. To do so, all the patients referred to the clinic could enter the study, provided that they met the inclusion criteria. The inclusion criteria of patients were as follows:

- Participants were selected from patients taking warfarin who referred to the clinic, regardless of their disease.
- Patients whose status was stable.
- Patients who were willing to participate in the project.
- Patients who had a smartphone with the Android operating system.
- Patients who were able to use the mobile application.
- Patients who required warfarin therapy for at least one year.
- The patients' gender was not considered.
- The patients' age was not considered.
- Patients who were mentally healthy.

The exclusion criteria of patients were as follows:

- Patients with unavailable or incomplete data regarding project implementation.
- Patients who required surgery.
- Patients who developed acute diseases.
- Patients who were unwilling to participate in the project.

According to the above-mentioned criteria, 7 patients were selected from those who referred to the clinic. These patients were from the three provinces. Patients were interviewed. They were asked about their level of education and how much they adhered to the physician's instructions in the usual treatment method and followed prescriptions on time.

The application was evaluated in terms of efficiency in maintaining the patients' INRs within the therapeutic range as well as the patients' TTR. The current study was conducted following a Before-After study design to evaluate the application efficiency. The required investigations were then performed and the information items required for recording during the study period were determined as well. Eventually, a special medical record form called *patients' medical and laboratory record form* was designed to store medical data as well as patients' INR test results during the two periods of before using the mobile application and after using the mobile application. The medical and laboratory record form can be seen in Figure 1.

Then, patients' medical and laboratory data were collected. The study medical data included sex, the start date for taking warfarin, age (in years), indications, target INR range, and the duration of time in which the patient required to be treated. The patients' laboratory data included the following information recorded at each visit: visit date, blood test date, INR result, type of complication, complication incidence date, new dosage, next blood test date, and record date. During the project implementation (both the Before and After periods), patients were supposed to refer to former laboratories, and the quality of laboratory tests was also supposed to be constant.

The evaluation of patients started from the Before period, and patients could move on to the After period, provided that at least four tests were performed on each patient. Besides, the condition for the completion of the After period was to perform at least four tests. In the Before period, patients were treated as usual, and in the After period, the XrinA mobile application was used to telecontrol oral anticoagulation therapy. In this application, there was a possibility to set up two-way communication between the patient and the physician via the Internet and send a notification. In each period, the ratio of the number of INRs within the therapeutic range to the total number of tests in that period was calculated and expressed in percentage. Therefore, for each period, the percentage of INRs within the therapeutic range was calculated and the results of the two periods were compared. Then, in both the Before and After periods, the patients' TTR was calculated and compared.

Results

This study aimed to evaluate the impact of using mHealth on warfarin PSM. The study was carried out following a Before-After study design. Seven patients entered the Before period and after performing at least four tests, they could enter the After period. Demographic information of patients is given in Tables 1 and 2.

Table 1. Demographic and Target INR Range of patients

Patient	Age (yr)	Low Range	High Range	Sex	Pathology
j	83	2	2.5	F	Pace maker
k	63	2	2.5	F	Atrial fibrillation proximal
l	54	2.5	3.5	F	Prosthetic heart valve
m	67	2	2.5	F	Coronary Artery Bypass Grafting (CABG)
n	64	2.5	3.5	F	Prosthetic heart valve
o	68	2.5	3	F	Prosthetic heart valve
p	30	3	3.5	F	Prosthetic heart valve

Table 2. Demographic and Educational level of patients

Variable		mean or n (%)
Demography		
	Age, years	61.3
	Female, n (%)	7 (100)
Educational level, n (%)		
	Less than a high school diploma, n (%)	2 (28.5)
	High school diploma, n (%)	3 (43)
	Associate's degree, n (%)	2 (28.5)

The factors contributing to patient warfarin uptake are listed in Table 3.

Table 3. Oral anticoagulant therapy (OAT)-requiring pathologies of patients

Pathology	n (%)
Atrial fibrillation proximal	1 (14.3)
Prosthetic heart valve	4 (57.1)
Pace maker	1 (14.3)
Coronary artery bypass grafting (CABG)	1 (14.3)

The patients' therapeutic range is presented in Table 4.

Table 4. Oral anticoagulant therapy (OAT)-Target INR Range of patients

Target INR Range	n (%)
2.0 – 2.5	3 (43)
2.5 – 3.0	1 (14)
2.5 – 3.5	2 (29)
3.0 – 3.5	1 (14)

The period of study ranged from 25/4/2018 to 22/5/2019. The study period including both the Before and After periods for each patient is given in Table 5.

Table 5. Study Duration

Patient	Before (Usual Care)			After (New Care)			Total Duration (Days)
	From	To	Duration (Days)	From	To	Duration (Days)	
j	31/07/2018	30/11/2018	122	30/11/2018	15/05/2019	166	288
k	27/05/2018	26/11/2018	183	26/11/2018	23/01/2019	58	241
l	25/04/2018	15/11/2018	204	15/11/2018	17/03/2019	122	326
m	21/09/2018	01/12/2018	71	01/12/2018	13/01/2019	43	114
n	14/08/2018	12/12/2018	120	12/12/2018	05/05/2019	144	264
o	31/07/2018	04/12/2018	126	04/12/2018	23/01/2019	50	176
p	22/09/2018	18/12/2018	87	18/12/2018	22/05/2019	155	242
All	25/04/2018	18/12/2018	913	15/11/2018	22/05/2019	738	1651

Result regarding the number of tests and the percentage of INRs within the therapeutic range for each patient is presented in Table 6.

Table 6. Tests in Range of Patients

Patient	Before (Usual Care)			After (New Care)			Growth Rate of Tests in Range After Using Software	The Effect of Using Software
	Total Number of Tests	Number of Tests in Range	% of Tests in Range	Total Number of Tests	Number of Tests in Range	% of Tests in Range		
j	11	2	18.18%	13	7	53.85%	+35.67%	Positive
k	7	4	57.14%	5	2	40%	-17.14%	Negative
l	6	3	50%	10	3	30%	-20%	Negative
m	5	3	60%	4	1	25%	-35%	Negative
n	9	1	11.11%	10	7	70%	+58.89%	Positive
o	8	2	25%	4	2	50%	+25%	Positive
p	20	0	0%	19	4	21.05%	+21.05%	Positive

Result regarding each patient’s TTR during the study is given in Table 7.

Table 7. TTR of Patients

Patient	Before (Usual Care)			After (New Care)			Growth Rate of TTR After Using Software	The Effect of Using Software
	Days Within Range	Total Days	TTR	Days Within Range	Total Days	TTR		
j	31.7	122	26.0%	80.2	166	48.3%	+22.3%	Positive
k	98.2	183.0	53.7%	33.8	58.0	58.3%	+4.6%	Positive
l	104.9	204.0	51.4%	66.1	122.0	54.2%	+2.8%	Positive
m	50.4	71.0	70.9%	22.4	43.0	52.0%	-18.9%	Negative
n	8.0	120.0	6.6%	90.0	144.0	62.5%	+55.9%	Positive
o	40.6	126.0	32.2%	22.9	50.0	45.7%	+13.5%	Positive
p	0.0	87.0	0.0%	44.6	155	28.8%	+28.8%	Positive

Discussion

Patient self-care covers a broad spectrum ranging from the lowest level to the highest level representing the full patient responsibility for the treatment, which means that at the lowest level of self-care, the patient participates to a lesser degree in taking care of himself/herself as compared to the health system, whereas at the highest level of self-care, the patient performs 100% self-care behavior and moves towards patient self-management (PSM).

On the one hand, nowadays, patients with chronic diseases are actively involved in their own treatment and have greater cooperation with the treatment team in this sense [1]. On the other hand, studies have shown that the accuracy of dose prescription determined using the computer to achieve the INR target level is not less than that of experienced medical staff prescription [17, 23, 24]; therefore, the determination of dose rate using computer software has received increased interest from physicians and medical staff day after day [15, 16]. Due to the set of these benefits, eHealth applications gain more popularity in this field and PSM is considered as the next step in the management of oral anticoagulation therapy [1].

The platform applied to self-management software includes both personal computers (PC) and mobile phones. It appears that PCs apply highly in medical centers, while mobile phones are extensively utilized for PSM. Because smartphones are almost always with the patient and possess the capability to set up two-way communications [25]. Therefore, self-management mobile applications pave the way for establishing continuous communication between the patient and the care team.

The whole study period including Before and After periods ranged from 25/4/2018 to 22/5/2019 for 13 months. The Before period lasted from 25/4/2018 to 18/12/2018 for 8 months and the After period lasted from 15/11/2018 to 22/5/2019 for 6 months. The start date of the After period was not a fixed date for all patients, and each patient moved on to the After period as they met its entry criteria (Table 5).

Comparing the Results of the Present Study with the Findings of Other Studies

In 18 studies [7, 8, 10, 15-17, 26-37], the impact of patient self-management of oral anticoagulation therapy using eHealth applications on the percentage of INRs within the therapeutic range and the percentage of TTR were investigated. Out of 18 studies on therapeutic outcomes, 16 studies showed that patient self-management using eHealth apps improved therapeutic outcomes.

Out of 5 studies [7, 8, 27, 30, 31] on INRs within the therapeutic range, 4 studies showed that patient self-management of oral anticoagulation therapy using eHealth applications increased the number of INRs within the therapeutic range. There was no negative impact on the number of INRs within the therapeutic range in any study. Regarding INR, the results of the present study indicated that the XrinA application increased the mean INRs within the therapeutic range by 9.78%; therefore, it is recommended to replace conventional methods with this method. However, it should be pointed out that according to other studies conducted in this field, 50% of major complications occurred when INR is within the therapeutic range [1]. In these circumstances, the use of this application by patients, facilitating access to the care team, can play an effective role in the prevention and reduction of injuries caused by complications and can be regarded as an appropriate alternative to conventional methods as well.

Out of 17 studies [7, 8, 10, 15-17, 26, 28-37] on TTR, 14 studies revealed that patient self-management of oral anticoagulation therapy using eHealth applications led to an improvement of TTR values. In most of these studies, it was found that patient self-management using applications increased TTR by 0.7 to 15.4%, so that compared to the conventional methods, the range of TTR increased from 53.2-72.7 to 63.3-80.2 in new methods. The results from the present study indicated that in the new method focusing on the XrinA application, the percentage of TTR ranged from 0-70.9 % to 28.8-62.5% as compared to the conventional methods, which led to a 15.57% increase in the percentage of TTR, indicating that patient self-management of oral anticoagulation therapy using XrinA application based on this index can also be considered as an appropriate alternative to conventional methods.

Comparing the Results from the After and Before Periods in the Current Study

The INRs within the therapeutic range and TTR of patients as well as their mean are given in Table 8.

Table 8 . Percentage of Tests in Range, TTR and Their's Means

Variable	Before (Usual Care)	After (New Care)
% of Tests in Range	0 – 60	21.05 – 70
TTR	0 – 70.9	28.8 – 62.5
The mean % of Tests in Range	31.63%	41.41%
Mean TTR	34.4%	49.97%

In the Before period, 0-60 % of patients' INRs were in the therapeutic range and the percentage of TTR ranged from 0% to 70.9%. In the After period, 21.05-70 % of patients' INRs were in the therapeutic range and the percentage of TTR ranged from 28.8% to 62.5%.

In the Before period, the mean percentage of INRs within the therapeutic range of patients and the mean TTR of patients were 31.63% and 34.4%, respectively. In the After period, the mean percentage of INRs within the therapeutic range of patients and the mean TTR of patients were 41.41% and 49.97%, respectively. In the After period, the mean INRs within the therapeutic range and the mean TTR increased by 9.78% and 15.57%, respectively. Moreover, the minimum percentage of INR tests within the therapeutic range and TTR, which were zero in the Before period, increased to 21.05% and 28.8%, respectively.

Concerning TTR results, other studies indicated that TTR can be considered as an appropriate alternative to previous models, provided that the percentage of TTR is not less than 60% in a management model and also there is at least 5 to 10% improvement in the percentage of TTR as well [10, 38]. As presented in reference [39], TTR was divided into three ranges: weak, medium and good. In the current study, 86% of patients were in the weak range, although the proportion of patients with weak TTR did not alter in the After period (Table 9). However, it should be noted that TTR increased by an average of 15.57% compared to the conventional method, indicating that the patient self-management of oral anticoagulation therapy using the XrinA application can be regarded as an appropriate alternative to conventional methods.

Table 9. Distribution of patients of the two OAT treatment groups (Before and After with the XrinA)

TTR	Before n (%)	After n (%)
Poor TTR: <60%	6 (86)	6 (86)
Moderate TTR: 60% – <75%	1 (14)	1 (14)
Good TTR: ≥75%	0 (0)	0 (0)

During interviews with patients, it was found that the main cause of low adherence among patients in the Before period was the forgetting of drug use times and more specifically, not performing tests on time. Significantly, the use of XrinA application increased patients' adherence. During the interview with the physician, it was revealed that another cause of being out of therapeutic range among patients was the culture of using herbal teas and subsequently the arbitrary use of herbal teas by the patients.

Conclusions

The study results indicated that the use of XrinA-based PSM improved therapeutic outcomes including the number of INRs within the therapeutic range and the percentage of TTR. However, there were some negative findings in some patients, revealing the necessity for proper application development and implementation and subsequent continuous evaluation.

Setting up communication between the patient and the care team was among the other capabilities of the XrinA application. In order to develop mHealth applications with more features and capabilities, it is necessary to organize a team with a combination of different experts in the fields of information technology (IT) and medicine possessing the capability of developing appropriate applications with full knowledge. It is, therefore, recommended that mobile technology, due to its pervasiveness, be utilized in further studies to improve patient self-management of oral anticoagulation therapy.

Declarations

Competing interests

The authors declare that there is no conflict of interest.

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Abbreviations

ACs: Anticoagulation Clinics

CDSS: Computerized Decision Support System

CRC: Class-Responsibility-Collaboration

CVD: CardioVascular Disease

eHealth: electronic Health

ERD: Entity Relationship Diagram

FAQs: Frequently Asked Questions

INRs: International Normalized Ratios

IP: Internet Protocol

IT: Information Technology

mHealth: mobile Health

NOACs: Novel Oral Anticoagulants

OAT: Oral Anticoagulant Therapy

PC: Personal Computer

POCT: Point-Of-Care Testing

PSM: Patient Self-Management

TTR: Time in Therapeutic Range

UI: User Interface

VKAs: Vitamin K Antagonists

References

1. Christensen TD. Self-management of oral anticoagulation therapy–methodological and clinical aspects. Dan Med Bull. 2011;58(5):B4284.
2. Hirsh J, Warkentin TE, Shaughnessy SG, Anand SS, Halperin JL, Raschke R, et al. HEparin and low-molecular-weight heparin mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. Chest. 2001;119(1_suppl):64S-94S.
3. Koopman MMW, Prandoni P, Piovella F, Ockelford PA, Brandjes DPM, van der Meer J, et al. Treatment of Venous Thrombosis with Intravenous Unfractionated Heparin Administered in the Hospital as Compared with Subcutaneous Low-Molecular-Weight Heparin Administered at Home. New England Journal of Medicine. 1996;334(11):682-7.
4. Levine M, Gent M, Hirsh J, Leclerc J, Anderson D, Weitz J, et al. A Comparison of Low-Molecular-Weight Heparin Administered Primarily at Home with Unfractionated Heparin Administered in the Hospital for Proximal Deep-Vein Thrombosis. New England Journal of Medicine. 1996;334(11):677-81.
5. Nutescu EA, Bathija S, Sharp LK, Gerber BS, Schumock GT, Fitzgibbon ML. Anticoagulation patient self-monitoring in the United States: Considerations for clinical practice adoption. Pharmacotherapy. 2011;31(12):1161-74.
6. Christensen TD, Grove EL, Nielsen PB, Larsen TB. Self-managed oral anticoagulant therapy: A call for implementation. Expert Review of Cardiovascular Therapy. 2016;14(3):255-7.
7. Bereznicki LR, Jackson SL, Peterson GM. Supervised patient self-testing of warfarin therapy using an online system. Journal of medical Internet research. 2013;15(7):e138.

8. Christensen H, Lauterlein JJ, Sørensen PD, Petersen ER, Madsen JS, Brandslund I. Home management of oral anticoagulation via telemedicine versus conventional hospital-based treatment. Telemedicine journal and e-health : the official journal of the American Telemedicine Association. 2011;17(3):169-76.
9. Heneghan CJ, Garcia-Alamino JM, Spencer EA, Ward AM, Perera R, Bankhead C, et al. Self-monitoring and self-management of oral anticoagulation. The Cochrane Library. 2016.
10. Ferrando F, Mira Y. Effective and Safe Management of Oral Anticoagulation Therapy in Patients Who Use the Internet-Accessed Telecontrol Tool SintromacWeb. Interactive journal of medical research. 2015;4(2):e10.
11. Barcellona D, Fenu L, Marongiu F. Point-of-care testing INR: an overview. Clin Chem Lab Med. 2017;55(6):800-5.
12. Gardiner C, Williams K, Longair I, Mackie IJ, Machin SJ, Cohen H. A randomised control trial of patient self-management of oral anticoagulation compared with patient self-testing. British journal of haematology. 2006;132(5):598-603.
13. De Caterina R, Husted S, Wallentin L, Andreotti F, Arnesen H, Bachmann F, et al. Vitamin K antagonists in heart disease: Current status and perspectives (Section III). Thrombosis and haemostasis. 2013;110(6):1087-107.
14. KIM YK, Nieuwlaat R, Connolly S, Schulman S, Meijer K, Raju N, et al. Effect of a simple two-step warfarin dosing algorithm on anticoagulant control as measured by time in therapeutic range: a pilot study. Journal of Thrombosis and Haemostasis. 2010;8(1):101-6.
15. Jowett S, Bryan S, Poller L, Van Den Besselaar AMHP, Van Der Meer FJM, Palareti G, et al. The cost-effectiveness of computer-assisted anticoagulant dosage: results from the European Action on Anticoagulation (EAA) multicentre study. Journal of Thrombosis and Haemostasis. 2009;7(9):1482-90.
16. Poller L, Keown M, Ibrahim S, Lowe G, Moia M, Turpie AG, et al. A multicentre randomised clinical endpoint study of parma 5 computer-assisted oral anticoagulant dosage. British Journal of Haematology. 2008;143(2):274-83.
17. Poller L, Shiach C, MacCallum P, Johansen A, Münster A, Magalhäes A, et al. Multicentre randomised study of computerised anticoagulant dosage. The Lancet. 1998;352(9139):1505-9.
18. Lee J-A, Nguyen AL, Berg J, Amin A, Bachman M, Guo Y, et al. Attitudes and Preferences on the Use of Mobile Health Technology and Health Games for Self-Management: Interviews With Older Adults on Anticoagulation Therapy. JMIR mHealth uHealth. 2014;2(3):e32.
19. Lee J-A, Evangelista LS, Moore AA, Juth V, Guo Y, Gago-Masague S, et al. Feasibility Study of a Mobile Health Intervention for Older Adults on Oral Anticoagulation Therapy. Gerontology and Geriatric Medicine. 2016;2:1-8.
20. Tideman PA, Tirimacco R, St John A, Roberts GW. How to manage warfarin therapy. Australian prescriber. 2015;38(2):44.
21. Naderi Haji M, Moghaddasi H, Sharif-Kashani B, Kazemi A, Rahimi F. Characteristics of software used in self-management of vitamin K antagonist therapy: A systematic review. European journal of cardiovascular nursing : journal of the Working Group on Cardiovascular Nursing of the European Society of Cardiology. 2019;18(5):358-65.

22. Haji MN, Kazemi A, Moghaddasi H, Sharif-Kashani B. The Results of Using Electronic Health Software for Self-Management of Vitamin K Antagonist Therapy - A Systematic Review. Biomedical Journal of Scientific & Technical Research. 2019;15(4):11469-76.
23. Ryan F, Byrne S, O'Shea S. Managing oral anticoagulation therapy: improving clinical outcomes. A review. Journal of clinical pharmacy and therapeutics. 2008;33(6):581-90.
24. Gillaizeau F, Chan E, Trinquart L, Colombet I, Walton RT, Rège-Walther M, et al. Computerized advice on drug dosage to improve prescribing practice. Cochrane Database of Systematic Reviews [Internet]. 2013; (11). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002894.pub3/abstract.
25. Gravenhorst F, Muaremi A, Bardram J, Grünerbl A, Mayora O, Wurzer G, et al. Mobile phones as medical devices in mental disorder treatment: an overview. Personal and Ubiquitous Computing. 2014:1-19.
26. Poller L, Keown M, Ibrahim S, Lowe G, Moia M, Turpie AG, et al. A multicentre randomised assessment of the DAWN AC computer-assisted oral anticoagulant dosage program. Thromb Haemost. 2009;101(3):487-94.
27. Poller L, Wright D, Rowlands M. Prospective comparative study of computer programs used for management of warfarin. Journal of clinical pathology. 1993;46(4):299-303.
28. Manotti C, Moia M, Palareti G, Pengo V, Ria L, Dettori AG. Effect of computer-aided management on the quality of treatment in anticoagulated patients: a prospective, randomized, multicenter trial of APROAT (Automated PRogram for Oral Anticoagulant Treatment). Haematologica. 2001;86(10):1060-70.
29. Dimberg I, Grzymala-Lubanski B, Hägerfelth A, Rosenqvist M, Svensson P, Själander A. Computerised assistance for warfarin dosage - Effects on treatment quality. European Journal of Internal Medicine. 2012;23(8):742-4.
30. Salvador CH, Ruiz-Sanchez A, González de Mingo MA, Carmona Rodríguez M, Carrasco MP, Sagredo PG, et al. Evaluation of a telemedicine-based service for the follow-up and monitoring of patients treated with oral anticoagulant therapy. IEEE transactions on information technology in biomedicine : a publication of the IEEE Engineering in Medicine and Biology Society. 2008;12(6):696-706.
31. Harper P, Pollock D. Improved anticoagulant control in patients using home international normalized ratio testing and decision support provided through the Internet. Internal medicine journal. 2011;41(4):332-7.
32. Ryan F, Byrne S, O'Shea S. Randomized controlled trial of supervised patient self-testing of warfarin therapy using an internet-based expert system. Journal of Thrombosis and Haemostasis. 2009;7(8):1284-90.
33. O'Shea SI, Arcasoy MO, Samsa G, Cummings SE, Thames EH, Surwit RS, et al. Direct-to-patient expert system and home INR monitoring improves control of oral anticoagulation. Journal of Thrombosis and Thrombolysis. 2008;26(1):14-21.
34. Matchar DB, Jacobson A, Dolor R, Edson R, Uyeda L, Phibbs CS, et al. Effect of home testing of international normalized ratio on clinical events. New England Journal of Medicine. 2010;363(17):1608-20.
35. Rasmussen RS, Corell P, Madsen P, Overgaard K. Effects of computer-assisted oral anticoagulant therapy. Thrombosis Journal. 2012;10.

36. Fitzmaurice DA, Hobbs FR, Murray ET, Holder RL, Allan TF, Rose PE. Oral anticoagulation management in primary care with the use of computerized decision support and near-patient testing: a randomized, controlled trial. Archives of Internal Medicine. 2000;160(15):2343-8.
37. Manotti C, Pattacini C, Quintavalla R, Tagliaferri A, Lombardi M, Tassoni M. Computer assisted anticoagulant therapy. Pathophysiology of haemostasis and thrombosis. 2003;33(5-6):366-72.
38. Fitzmaurice D, Murray E, McCahon D, Holder R, Raftery J, Hussain S, et al. Self management of oral anticoagulation: randomised trial. Bmj. 2005;331(7524):1057.
39. Bussey HI. Transforming oral anticoagulation by combining international normalized ratio (INR) self testing and online automated management. Journal of thrombosis and thrombolysis. 2011;31(3):265-74.

Figures

Warfarin Patient Record

Physician and medical center information

Doctor Name: | Name of medical center: | Phone number of the medical center:

Patient clinical and laboratory data

Name: | Last Name: | Phone model: | Mobile Phone Number: | Home phone number:

Gender: ☐ Female ☐ Male | Starting date of warfarin: | Age (years): | National Code:

Indications: ☐ DVT/PE ☐ prosthetic heart valve ☐ Other: ☐ atrial fibrillation ☐ thrombophilia ☐ intracardiac thrombus | Target INR Range: ☐ 2.0 – 3.0 ☐ 2.5 – 3.5 ☐ Other: | Duration: ☐ lifelong ☐ reassess, when:

Row	Date of visit	Date of blood test	Result of INR	Type of complication	Date of complication	New dose	Next blood test date	Date of record	Signature
1				☐ Bleeding ☐ Multiple / extensive bruising					
2				☐ Bleeding ☐ Multiple / extensive bruising					
3				☐ Bleeding ☐ Multiple / extensive bruising					
4				☐ Bleeding ☐ Multiple / extensive bruising					
5				☐ Bleeding ☐ Multiple / extensive bruising					
6				☐ Bleeding ☐ Multiple / extensive bruising					
7				☐ Bleeding ☐ Multiple / extensive bruising					
8				☐ Bleeding ☐ Multiple / extensive bruising					
9				☐ Bleeding ☐ Multiple / extensive bruising					
10				☐ Bleeding ☐ Multiple / extensive bruising					

* Multiple / extensive bruising: The area of bruising is about half the size of the palm or more than three in number
* Dosage based on multiples of 1/4 warfarin 5 mg tablet

Figure 1

Patients' medical and laboratory record form

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Additionalfile1PRISMA2009ChecklistMSWord.doc
- Additionalfile2SearchStrategy.docx
- Additionalfile3TheSearchFlowDiagram.docx