Electronic Counselling for Oral Anticoagulant Patients

Khulud Tariq Kadi

A thesis submitted for the degree of Master in Science

School of Pharmacy and Pharmaceutical Sciences
Trinity College Dublin

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Declaration

I declare that this thesis has not been submitted as an exercise for a degree at this or any other university and it is entirely my own work, except where duly acknowledged.

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Signed: ______________________

Khulud Tariq Kadi
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Abbreviations

AF  Atrial Fibrillation.
ACS  Acute Coronary Syndromes.
AKA  Anticoagulant Knowledge Assessment test.
APS  Antiphospholipid Syndrome.
3A4  Cytochrome P450 3A4.
BMI  Body Mass Index.
CPAS  Clinical Pharmacy Anticoagulation Service.
DOACs  Direct Oral Anticoagulants.
DP  Drugs Payment scheme.
DVT  Deep Vein Thrombosis.
ECG  Electrocardiography.
ECT  Ecarin Clotting Time.
FDA  Food and Drug Administration.
GMS  General Medical Services.
GP  General Practitioner.
GSES  Generalized Self- Efficacy Scale.
INR  International Normalized Ratio.
ISTH  International Society for Thrombosis and Haemostasis.
KR  Knowledge Retention questionnaire.
LMW heparin  Low molecular weight heparin.
LTI  Long-Term Illness scheme.
NOACs  New/ Novel Oral Anticoagulants.
OAC  Oral Anticoagulant.
OAK  Oral Anticoagulants Knowledge test.
PE  Pulmonary Embolism.
P-gp  P glycoprotein.
PSM  Patient Self-Management.
POC  Point-of-Care.
POCT  Point-of-Care Test.
PSM  Patient Self-Management.
PST  Patient Self-Testing.
QoL  Quality of Life.
RCT  Randomized Controlled Trial.
SSC  Scientific and Standardization Committee.
TREAT  TRIal of an Educational intervention on patients’ knowledge of Atrial fibrillation and anticoagulant therapy, INR control, and outcome of Treatment with warfarin.
TSOACs  Target-Specific Oral Anticoagulant agents.
TT  Thrombin Time.
TTR  Time in Therapeutic Range.
UFH  Unfractionated Heparin.
UNCMC  University of North Carolina Medical Center.
VKAs  Vitamin K Antagonists.
VTE  Venous Thromboembolism.
Summary

Education is an essential part of care for patients taking oral anticoagulants. However, it may be time-consuming for health care providers and overwhelming for patients, and hence sometimes suboptimal. Technology-based education programs have the potential to overcome some of the problems relating to patient education and thus help to minimize therapy complications and improve clinical outcomes. The principal purposes of this study were to identify and evaluate research on electronic education interventions for warfarin patients, and to create and pilot electronic education programs for warfarin and DOAC patients.

Chapter 1 provides general background information on coagulation, anticoagulants and patient education.

Chapter 2 describes a systematic review, to our knowledge the first to evaluate technology-based educational interventions for warfarin patients. Searches were conducted of the Cochrane Library (CENTRAL), Ovid (MEDLINE), PubMed, CINAHL Plus (EBSCOhost), ERIC ProQuest, and Web of Science databases, as well as of US and EU clinical trials databases, for randomized controlled trials evaluating the effect of any electronic education intervention alone or in combination with other self-management techniques, in warfarin patients. The searches included studies published in English without date restrictions. Manual searches of reference lists in relevant publications were also conducted. All identified references were screened for inclusion within Endnote software. The Cochrane Collaboration’s Review Manager 5.3 (Rev Man 2014) software was then used for further data extraction and analysis. Risk of bias was assessed using the Cochrane ‘Risk of bias’ tool.

Three randomized control trials and one ongoing study were identified. While they showed positive effects for electronic education of warfarin patients, the small size and heterogeneous nature of the identified studies mean the findings are limited in their value, and meta-analysis was not possible. More adequately powered, good quality, randomized, controlled studies are required in this area.

Chapter 3 describes the development and piloting of an electronic tool to educate and assess patients’ knowledge regarding their warfarin therapy. The tool was developed using Articulate 360 software and consisted of three main sections: a pre-education knowledge test (a previously validated anticoagulant knowledge test), an education section, and repetition of the knowledge test. It was piloted in the community pharmacy on English-speaking adult patients receiving warfarin who could use a suitable electronic device.
A total of 56 patients participated in the pilot. 35/56 (62.5%) passed the knowledge test before the education program and this showed a statistically significant increase to 51/56 (91.1%) after the education program, demonstrating the utility of the tool in the short-term. Feedback to enhance the electronic tool was also received. The results of this pilot have laid the foundation for a future more comprehensive study incorporating long term follow up and a wider range of outcome measures.

Chapter 4 concerns the development and piloting of an electronic education program for patients taking direct-acting oral anticoagulants (DOACs), which are increasingly being prescribed owing to their advantages over warfarin: They can be given in fixed doses, have fewer interactions with food or other drugs, a wide therapeutic window and do not require monitoring as closely as warfarin. As for the warfarin education tool, the DOAC program comprised educational material preceded and followed by knowledge tests. However, in this case the education component took the form of a dialogue between a pharmacist and patient, with points of interactivity where the patient selected material relevant to the DOAC he/she had been prescribed. Baseline adherence was established through the incorporation of the Morisky 8-item medication adherence scale (MMAS-8) into the program before the education component. The pre- and post-education knowledge test comprised relevant questions from the same anticoagulation knowledge test as that used in the warfarin education program.

The program was evaluated in community pharmacies and by pharmacists in the pharmacist-led outpatient anticoagulation clinic of a major Dublin hospital. Eligible patients were English-speaking adults who were capable of using appropriate electronic devices.

A total of 53 patients enrolled in the pilot. 43/53 (81.1%) patients passed the test before the education program, and this showed a significant increase to 50/53 (94.3%) after education. In the MMAS-8 item questionnaire only 4 patients showed a low level of self-reported baseline adherence, 23 patients had a medium level of adherence, and 26 patients had a high adherence level.

This pilot study confirmed that the tools were capable of being used in the workplace environment and of enhancing patient knowledge in the short term. Feedback was received on potential improvements, in particular to enhance the personalization of the education experience for individual patients, enabling future work to assess a refined intervention in a larger and longer duration randomized controlled trial with more comprehensive outcome measures.

Chapter 5 explores the overall findings, and sets out the future work that can build upon the studies described here.
1. Introduction

1.1. OVERVIEW OF ANTICOAGULANT THERAPY

1.1.1. Blood coagulation cascade

The coagulation cascade consists of two pathways: the intrinsic, or contact activation pathway and the extrinsic, or tissue factor pathway. (1) Blood coagulates because of the transformation of soluble fibrinogen into insoluble fibrin by the enzyme thrombin. (2) A series of reactions happens throughout the coagulation cascade that causes the conversion of inactive enzyme precursors to their active forms, and these active forms catalyze the subsequent reactions in the cascade. (1) Endothelial damage results in activation of the extrinsic pathway of the clotting cascade by the release of thromboplastin (tissue factor). This tissue factor converts factor VII in the presence of Ca$^{2+}$ to factor VIIa, which mediates the activation of factor X. (1, 3) The intrinsic pathway of the clotting cascade is activated via the exposure of factor XII to subendothelial components exposed during vessel injury; this pathway mediates factor X activation through a chain of events started by factor XI. (3) Once both the extrinsic and intrinsic pathways are stimulated, they activate the common pathway of the clotting cascade, which is responsible for the formation of a fibrin mesh on the damaged vessel wall, through factor X and the activated forms of factors V and VIII that serve independently to accelerate this process. (1, 3) The last steps include conversion of factor II (prothrombin) to factor IIa (thrombin), resulting in the formation of a stable fibrin clot. (3) See Figure 1.1.
1. Introduction

Figure 1.1: Simplified clotting cascade and respective anticoagulant targets. (3)

1.1.2. Anticoagulant classification

1.1.2.1. Parenteral anticoagulants

Parenteral anticoagulants may be divided into direct and indirect anticoagulants.

Indirect parenteral anticoagulants:

These are drugs whose activity is mediated by plasma cofactors. They have little or no intrinsic anticoagulant activity and exert their anticoagulant activity by potentiating antithrombin (AT), an endogenous inhibitor of various activated clotting factors. (4, 5) The indirect parenteral anticoagulants include heparin (unfractionated heparin), low-molecular-weight-heparins (LMWHs), fondaparinux, and danaparoid. (4, 5) LMWHs include enoxaparin, dalteparin, and tinzaparinux. (2)

Direct parenteral anticoagulants:

These drugs do not require plasma cofactors to express their activity. (4, 5) The direct parenteral anticoagulants in current use all target thrombin, and include recombinant hirudins, bivalirudin, and argatroban. (4, 5)
1. Introduction

1.1.2.2. Oral anticoagulants

Oral anticoagulants may be classified into two categories: vitamin K antagonists and direct oral anticoagulants.

**Vitamin K antagonists** include: dicoumarol, phenindione, warfarin, phenprocoumon, acenocoumarol, ethyl biscoumacetate, clorindione, diphenadione, ticlopidine, and fluindione. (6)

**Direct oral anticoagulants (DOACs)** include direct thrombin inhibitors such as dabigatran and direct factor Xa inhibitors such as rivaroxaban, apixaban, and edoxaban. (7)

More information about warfarin’s and DOACs’ indications, mechanisms of action, pharmacology, adverse effects, drug interactions, monitoring, and antidotes can be found in section 1.2 and section 1.3.

1.1.3. Oral anticoagulant therapy

The purpose of oral anticoagulant therapy and its main use is to prevent the formation of a thrombus, or the extension of an existing thrombus in the slower-moving venous side of the circulation. (8, 9) There are several disorders for which oral anticoagulants play a key role in treatment, including venous thromboembolism (VTE), comprising both deep vein thrombosis (DVT) and pulmonary embolism (PE), atrial fibrillation (AF), acute coronary syndromes (ACS), valve disease and endocarditis, and conditions associated with a raised risk of ischemic stroke. (1) However, the two major disorders prompting coagulation therapy are venous thromboembolism and atrial fibrillation. (8)
1. Introduction

1.2. OVERVIEW OF WARFARIN

Warfarin, a coumarin derivative, is one of the oral anticoagulants (vitamin K antagonists) which has the potential to prevent dangerous blood clots that may lead to heart attacks, strokes or even death. (10) However, it is also one of the main contributors to drug-related morbidity and mortality and for that reason it is considered a high alert medication. (10)

1.2.1. Mechanism of action

As already noted, warfarin is a coumarin derivative (vitamin K antagonist). It is known to interfere with:

- The cyclic interconversion of vitamin K and its 2,3 epoxide (vitamin K epoxide) to produce an anticoagulant effect by limiting hepatic production of the biologically active vitamin K-dependent clotting factors (activated factors II, VII, IX, and X). (11-13) In normal circumstances the precursors of these factors undergo a carboxylation reaction to be converted to their activated forms. As warfarin interferes with this reaction, the reduction in the amount and activity of these factors produces the anticoagulant response. (11-13)

- The carboxylation of Gla proteins synthesized in bone. (11, 13) These effects contribute to fetal bone abnormalities when pregnant women are treated with warfarin, but there is no evidence about the direct effects of warfarin on bone metabolism when administered to children or adults. (11, 13)

- The production of the body’s natural anticoagulants, protein C and protein S, and it can therefore sometimes exert a procoagulant response. (12) Protein C has a short half-life similar to factor VIIa which is 6 hours, so the immediate effect of warfarin is to deplete the procoagulant factor VII and anticoagulant protein C, which can paradoxically create a transient hypercoagulable state due to residual activity of the longer half-life procoagulants in the face of protein C depletion. (2) For this reason, it is necessary to use unfractionated heparin (UFH) or low molecular weight heparin in patients with active hypercoagulable states such as acute DVT or PE, to achieve immediate anticoagulation until adequate warfarin-induced depletion of the procoagulant clotting factors is achieved, and the duration of this overlapping therapy is generally 5–7 days. (2)
1. Introduction

1.2.2. Pharmacology of warfarin

Warfarin is generally administered as the sodium salt and has 100% oral bioavailability. (2) Warfarin is a racemic mixture of two active isomers, the R and S forms, in roughly equal proportions. (11) This racemic mixture has a long half-life in plasma (approximately 36 to 42 hours), and over 99% of racemic warfarin is bound to plasma proteins (mainly albumin), and accumulates in the liver where different pathways metabolically transform the two isomers. (2, 11, 12) The levorotatory S-isomer is four times more potent than the dextrorotatory R-isomer. (2) The hepatic metabolism of the two warfarin isomers are different: The S-isomer of warfarin is metabolized by cytochrome P450 2C9 (and to a lesser degree by P450 3A4) and is eliminated in the bile, while the R-isomer is metabolized by cytochrome P450 1A2 and P450 3A4 and is excreted in the urine as inactive metabolites. (12) The anticoagulant effect of warfarin is influenced by pharmacokinetic factors, including drug interactions that affect warfarin’s absorption or metabolic clearance, and pharmacodynamic factors that alter the hemostatic response to given concentrations of the drug. (11)

1.2.3. Indications

Warfarin’s indications include a wide range of clinical conditions such as venous thromboembolism (VTE), antiphospholipid syndrome (APS), atrial fibrillation (AF), cardioversion, valvular heart disease and prosthetic valves (i.e. mitral stenosis or regurgitation, mechanical prosthetic heart valves, and bio-prosthetic heart valves), peripheral vascular disease, and myocardial infarction and cardiomyopathy. (14, 15)

1.2.4. Complications related to warfarin use (adverse effects)

The most common and the main complication of warfarin therapy is bleeding. (13, 16) It is most likely to occur when the INR is too high. (10) The bleeding risks associated with warfarin use also relate to patient factors including age, a prior bleeding history and specific comorbidities. Older patients are more sensitive in general to the anticoagulant effect of warfarin, so in this case they require a lower mean daily dose than younger patients. (16, 17) The risk of bleeding is reduced by regularly monitoring the INR, ensuring the patient knows the action of warfarin, and understands how to recognize the signs of bleeding. (18) Another side effect of warfarin worth noting is skin necrosis; it is an uncommon complication, and it occurs in up to 0.1% of patients under warfarin therapy. (13, 19) The risk of skin necrosis occurring increases in patients with protein C or protein S deficiency, but the factors that determine which warfarin patients will experience the side effect are unclear. (19, 20) Thrombosis, hypersensitivity, haemorrhage, factor VII deficiency, protein C deficiency, and a direct toxic effect of warfarin are all suggested
mechanisms, but the precise mechanism of this side effect is still not clearly understood. (19) Furthermore, other adverse effects associated with warfarin use are: purple toes syndrome, alopecia, diarrhea, hepatic dysfunction, jaundice, nausea, pancreatitis, purpura, pyrexia, rash, and vomiting. (20)

1.2.5. Drug interactions

The most severe interactions with warfarin are those that affect the anticoagulant effect and the risk of bleeding. (2) Warfarin interactions can be considered to fall into two categories: pharmacokinetic and pharmacodynamic interactions. (12, 21) Pharmacokinetic mechanisms for interactions involve the way the body handles warfarin, and mainly include cytochrome P450 CYP2C9 enzyme induction, enzyme inhibition, and reduced plasma protein binding, whereas pharmacodynamic mechanisms for interactions include synergism (impaired hemostasis, reduced clotting factor synthesis, as in hepatic disease), competitive antagonism (vitamin K), and an altered physiologic control loop for vitamin K (hereditary resistance to oral anticoagulants). (2, 21) In routine practice, the most dangerous of these interactions tend to be the pharmacokinetic interactions. (2) The most widely mentioned example is cholestyramine. (12, 13)

Importantly, pharmacokinetic interactions result in a change in the INR and so they are easily monitored. (21) This is unlike pharmacodynamic interactions where the patient may have bleeding with no significant change in the INR. (21) In this situation, monitoring of the INR is not a useful predictor of bleeding. (21)

The numerous interactions of warfarin include food-drug interactions (diet), which may also be classified as pharmacokinetic interaction (for example, with cranberry and cranberry juice, grapefruit, green tea, chamomile, soybeans or soy milk, mango, ginseng, St. John’s wort, and ginkgo biloba) and/or pharmacodynamic interactions (for example, with green leafy vegetables, ginseng, and ginkgo biloba). (15, 22) Taking the interaction with cranberry juice as an example of a pharmacokinetic interactions, this drink alters CYP2C9 and 3A4 activity by inhibiting the activity of CYP2C9, which is the primary isoenzyme involved in the metabolism of S-warfarin. (15, 22) The moderate daily consumption of cranberry juice has little impact on PT-INR (increase in INR). In contrast, taking the interaction with green, leafy vegetables and certain vegetable oils as examples of pharmacodynamic interactions, they contain significant amounts of vitamin K, and their consumption in excess may lead to a decreased PT-INR. (15, 22)
1. Introduction

In terms of clinical significance, one study found that there is no convincing evidence at the present time to indicate that any food or nutrient other than vitamin K interacts significantly with warfarin, and that only two natural substances in common herbal medicines; St. John’s wort through the induction of CYP2C9 and possibly ginseng, have been proven to interact with warfarin’s anticoagulant action. (23)

Drug-drug interactions are numerous: for example, drugs that may increase INR such as macrolide antibiotics, imidazole antifungals, sulfamethoxazole/trimethoprim, amiodarone, statins, and some non-steroidal anti-inflammatory drugs. (18) Warfarin’s effects are also affected by weight loss or gain, and excessive drinking of alcohol. (18)

Medications that influence clotting such as other anticoagulants, antiplatelets, nonsteroidal anti-inflammatory drugs (NSAIDs), and selective serotonin reuptake inhibitors (SSRIs) will increase the risk of bleeding even when there is no specific drug-drug interaction. (24) The antibiotic drugs are one of the most common medication classes that have drug interactions with warfarin. (24) More examples of warfarin’s drug interactions, their mechanisms and effects are summarized in Table 1.1 which is adapted from Nutescu et al., 2016. (25)

Furthermore, there are various disease states and patient conditions which affect patients’ sensitivity to warfarin, and these should be considered during the initiation of warfarin therapy when the starting dose of warfarin needs to be determined. (25) Also, in later stages of warfarin therapy, the subsequent onset, exacerbation, or improvement in these conditions may lead to changes in the maintenance dose requirements of warfarin. (25) Example of these diseases and conditions include advanced age, alcohol use, chewing tobacco, cigarette smoking, clinical congestive heart failure, diarrhea, fever, following heart valve replacement, hemodialysis, hepatic disease, hypoalbuminemia, nutritional status, pregnancy/lactation, renal disease, and thyroid disease. (25)
1. Introduction

Table 1.1: Examples of warfarin drug interactions by mechanism and effect on INR; adapted from Nutescu et al., 2016. (25)

<table>
<thead>
<tr>
<th>Category</th>
<th>Mechanism</th>
<th>Effect</th>
<th>Common examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacodynamic interactions</td>
<td>Increased synthesis of clotting factors</td>
<td>Decrease INR</td>
<td>Vitamin K</td>
</tr>
<tr>
<td></td>
<td>Decreased synthesis of clotting factors</td>
<td>Increase INR</td>
<td>Cephalosporins</td>
</tr>
<tr>
<td></td>
<td>Reduced catabolism of clotting factors</td>
<td>Decrease INR</td>
<td>Methimazole</td>
</tr>
<tr>
<td></td>
<td>Increased catabolism of clotting factors</td>
<td>Increase INR</td>
<td>Propylthiouracil</td>
</tr>
<tr>
<td></td>
<td>Impaired vitamin K production by gut flora</td>
<td>Increase INR</td>
<td>Aminoglycosides</td>
</tr>
<tr>
<td></td>
<td>Additive anticoagulant response</td>
<td>Increase bleeding risk without influencing INR</td>
<td>Anticoagulants</td>
</tr>
<tr>
<td></td>
<td>Concurrent antiplatelet therapy</td>
<td>Increase bleeding risk without influencing INR</td>
<td>Antiplatelet agents</td>
</tr>
<tr>
<td>Pharmacokinetic interactions</td>
<td>Induction of warfarin metabolism</td>
<td>Decrease INR</td>
<td>Barbiturates, Carbamazepine, Nafcillin, Rifampin</td>
</tr>
<tr>
<td></td>
<td>Reduced absorption of warfarin</td>
<td>Decrease INR</td>
<td>Cholestyramine, Colestipol</td>
</tr>
<tr>
<td></td>
<td>Inhibition of warfarin metabolism</td>
<td>Increase INR</td>
<td>Amiodarone, Azole antifungals, Fluoroquinolone, Antibiotics, Macrolide antibiotics, Metronidazole, Sulfa antibiotics</td>
</tr>
</tbody>
</table>
1. Introduction

1.2.6. Clinical outcome measures

Due to warfarin's complex pharmacokinetic and pharmacodynamic characteristics and its narrow therapeutic window, routine laboratory monitoring and systematic oversight are required to accomplish optimal clinical outcomes and minimize unwanted drug side effects. (26)

1.2.6.1. International normalized ratio (INR) and Prothrombin time (PT)

The INR was developed in 1982 and adopted by the World Health Organization. (12, 27) The degree of anticoagulation was calculated from the prothrombin time and expressed as the international normalized ratio (INR). (28) The INR was introduced into clinical practice to monitor warfarin therapy due to the highly variable sensitivities of tissue thromboplastin reagents utilized to implement prothrombin tests. (29)

The two tests which assess the “global” function of the extrinsic or intrinsic clotting pathways are the prothrombin time (PT) and activated partial thromboplastin time (APTT) tests. The PT measures the extrinsic coagulation pathway, while the APTT measures the effectiveness of the intrinsic coagulation pathway. (30) The PT/INR and APTT tests are more often used for monitoring anticoagulant therapy than for assessing secondary haemostasis, with the PT/INR primarily used to monitor VKA therapy and the APTT to monitor UH. (31) These PT and APTT tests results are highly dependent on the combination of reagent and instrumentation used. (30)

The PT is sensitive to changes in the serum concentrations of the vitamin K dependent clotting factors, as it responds to the reduction of three of the four vitamin K–dependent procoagulant clotting factors (II, VII, and X) which are reduced by warfarin at a rate proportionate to their respective half-lives. (13, 25) The PT monitoring of warfarin treatment is very inaccurate when expressed as a PT ratio (calculated as a simple ratio of the patient’s plasma value over that of normal control plasma) because thromboplastins can vary notably in their responsiveness to warfarin. (13) Also, due to the considerable variability in their ability to detect the clotting defect induced by warfarin, the World Health Organization developed a system to standardize test results as any commercial reagent batch produced by any manufacturer is assigned an International Sensitivity Index (ISI) that describes its comparison to an international reference thromboplastin, which has an ISI of 1.0. (25) In addition, the identification of these deficiencies in PT monitoring motivated the development of the INR standard for monitoring oral anticoagulant therapy, and using this standard improved the safety of oral anticoagulant therapy and facilitated ease of monitoring. The INR calibration model is used to standardize reporting by converting the PT ratio measured with the local thromboplastin into an INR. (13)
1. Introduction

The ISI is utilized to mathematically convert prothrombin time in seconds to calculate the INR using the formula below: (25)

\[
\text{INR} = \left\{ \frac{PT_{\text{patients}}}{PT_{\text{mean normal}}} \right\} \text{ISI}
\]

where:

- \(PT_{\text{patients}}\): measured prothrombin time.

- \(PT_{\text{mean normal}}\): geometric mean PT of the reference range.

- ISI: International Sensitivity Index, specific to each reagent-instrument combination.

Inappropriate management of warfarin can lead to subtherapeutic or supratherapeutic INR values, and this leads to an increase in the risk of acute or recurrent thromboembolic or bleeding episodes. (12) The target therapeutic INR for most indications ranges from 2.0 to 3.0, except when warfarin is used as secondary prevention after a myocardial infarction or in the case of high-risk patients with mechanical prosthetic heart valves, in which cases the target INR ranges from 2.5 to 3.5. (11, 12) Also, some patients with thrombosis and the antiphospholipid syndrome may need a higher INR range than 2.0 to 3.0. (11)

1.2.6.2. Point-of-care testing (POCT)

Point-of-care testing is also known as near-patient testing, on-site monitoring, and decentralized testing. (32) It is valuable for monitoring, as point-of-care INR testing can be done in general practice, in other locations than hospital laboratories such as in pharmacies, or by patients themselves. (18) This way of testing the INR is more convenient for patients than visiting the anticoagulation clinic in a pathology practice or a hospital. (18) It is important for the performance of point of care monitors to be validated in order to ensure accurate information is available to support clinical decisions. In the past, a study of two widely used POCT monitors (CoaguChek and Rapid-PointCoag) revealed a noticeable mean difference from the "true INR" obtained on the same plasma samples (15.2%) and a considerable difference (21.3%) between the displayed INR on the two systems. (27)

The development and improvement of point-of-care (POC) instruments have allowed appropriately selected patients to carry out their INR testing at home (patient self-testing or PST). In some cases patients may even manage their warfarin dose adjustments (patient self-management; PSM), having either received specific dose instructions from their health care
1. Introduction

provider based on patient self-testing, or making their own dose choices according to a protocol. (26, 33) With patient self-testing and self-management strategies the patients do not need to travel for routine INR monitoring tests. This allows for more frequent testing, which has been associated with improved time in therapeutic range (TTR) in selected patient groups and permits the patient to be more involved in their care. (26)

1.2.7. Reversal agents (Antidotes)

The excessive anticoagulant effect of warfarin and the uncontrolled bleeding related to warfarin use can be reversed by cessation of the drug and administration of oral or parenteral vitamin K1 (phytonadione), fresh-frozen plasma, prothrombin complex concentrates, or recombinant factor VIIa (rFVIIa). (2)

1.2.8. Advantages and disadvantages

The vitamin K antagonists have been widely used since the 1940s, when warfarin was first established. Warfarin is the most commonly used vitamin K antagonist, and it has been available for a long time, meaning there is significant clinical experience of its use. (34-36) It also has an antidote: vitamin K such as prothrombin complex concentrate product, which can antagonise its effect in case of emergency situations. (35) It is also worth noting that from an economic point of view it is a cheap drug. (35). Table 1.2 compares the prices of various warfarin strengths with the prices of DOACs currently on the market in Ireland. (37-40) However, it should be noted that these prices do not take into account the costs associated with monitoring therapy. While the variation in monitoring frequency for patients with different medical conditions and at different stages of therapy (e.g. treatment initiation versus stable patients on longstanding treatment) (41) preclude accurate estimates of monitoring costs, on balance these would be expected to be significantly higher for warfarin than for the DOACs, and this should be taken into account in considering overall treatment expenses.
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Table 1.2: Comparison of warfarin and DOAC prices (37-40)

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Strength</th>
<th>quantity</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Warfarin (Warfarin Teva)</strong></td>
<td>1 mg</td>
<td>100 tablets</td>
<td>€3.11</td>
</tr>
<tr>
<td></td>
<td>3 mg</td>
<td>100 tablets</td>
<td>€5.08</td>
</tr>
<tr>
<td></td>
<td>5 mg</td>
<td>100 tablets</td>
<td>€7.18</td>
</tr>
<tr>
<td><strong>Rivaroxaban (Xarelto)</strong></td>
<td>10 mg</td>
<td>30 tablets</td>
<td>€66.45</td>
</tr>
<tr>
<td></td>
<td>15 mg</td>
<td>28 tablets</td>
<td>€64.11</td>
</tr>
<tr>
<td></td>
<td>15 mg</td>
<td>42 tablets</td>
<td>€96.16</td>
</tr>
<tr>
<td></td>
<td>20 mg</td>
<td>28 tablets</td>
<td>€64.11</td>
</tr>
<tr>
<td><strong>Apixaban (Eliquis)</strong></td>
<td>2.5 mg</td>
<td>20 tablets</td>
<td>€24.52</td>
</tr>
<tr>
<td></td>
<td>2.5 mg</td>
<td>60 tablets</td>
<td>€67.34</td>
</tr>
<tr>
<td></td>
<td>5 mg</td>
<td>56 tablets</td>
<td>€63.06</td>
</tr>
<tr>
<td></td>
<td>5 mg</td>
<td>28 tablets</td>
<td>€31.53</td>
</tr>
<tr>
<td><strong>Edoxaban (Lixiana)</strong></td>
<td>15 mg</td>
<td>10 tablets</td>
<td>€21.53</td>
</tr>
<tr>
<td></td>
<td>30 mg</td>
<td>28 tablets</td>
<td>€60.44</td>
</tr>
<tr>
<td></td>
<td>60 mg</td>
<td>28 tablets</td>
<td>€60.44</td>
</tr>
</tbody>
</table>

On the other hand, warfarin has several disadvantages. For example, it has a narrow therapeutic index, slow offset and delayed onset of action which need bridging therapy with another anticoagulant agent like low-molecular-weight heparin if immediate treatment is indicated, multiple drug-drug interactions, several food-drug interactions (interactions with dietary vitamin K intake), it commonly requires frequent dose adjustments, it has limitations secondary to genetics, and there is a requirement for regular blood test monitoring. (34, 35) These factors can be reviewed in subsections 1.1.5 and 1.1.6. All these unfavourable factors place a heavy load on patients and healthcare professionals, with implications for time and adherence to treatment, so the development of new agents to overcome these drawbacks was desirable. (34, 35)
1.4. OVERVIEW OF DIRECT ORAL ANTICOAGULANTS (DOACS)

This new class of anticoagulants has been described using various terms: Novel oral anticoagulants or new oral anticoagulants (NOACs), non-vitamin K antagonist oral anticoagulants (NOACs), target-specific oral anticoagulant agents (TSoACs), or direct oral anticoagulants (DOACs). (42, 43) However, DOACs was the recommended term from the Control of Anticoagulation Scientific and Standardization Committee (SSC) of the International Society on Thrombosis and Haemostasis (ISTH). (42, 43) They recommended that a single term be used consistently because the use of various terms and abbreviations can result in fragmentation of the medical literature, and confusion between providers and patients. The terms incorporating ‘new’ or ‘novel’ were also considered to be potentially confusing since with the passage of time they would not be new or novel any more. (43) However, the European Society of Cardiology (ESC) Working Group on Thrombosis Task Force on Anticoagulants in Heart Disease recommended keeping the well-known “NOACs” acronym to signify “Non-vitamin K antagonist Oral Anticoagulants.” (44) Recently, DOACs have been proven as an effective and safe alternative for the vitamin K antagonists (VKAs). (45-47) DOACs can overcome many of the disadvantages of traditional anticoagulants and for that reason they are one of the prominent developments in the recent practice of medicine. (48)

1.4.1. DOAC drug types

These oral anticoagulants include direct thrombin inhibitors: dabigatran etexilate, which inhibits thrombin, and factor Xa inhibitors: rivaroxaban, apixaban, and edoxaban, which inhibit factor Xa. (44, 49)

1.4.2. Mechanism of action

1.4.2.1. Direct thrombin inhibitors (dabigatran etexilate)

Dabigatran is a potent, competitive direct thrombin inhibitor, that reversibly and specifically binds to both clot-bound and free thrombin, in addition to inhibiting thrombin-induced platelet aggregation. (25)

1.4.2.2. Factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban)

The Factor-Xa inhibitors; apixaban, rivaroxaban and edoxaban, have a similar mechanism of action; they are competitive, selective and potent direct Factor-Xa inhibitors, and they bind in a reversible manner to the active site of both free-floating Factor-Xa and Factor-Xa within the
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Prothrombinase complex, relieving thrombin generation. (25) In addition, these drugs are not prodrugs and do not require activation. (25)

1.4.3. DOAC pharmacology

1.4.3.1. Dabigatran etexilate

Dabigatran etexilate is a prodrug of dabigatran with a bioavailability of 6.5%. (50) It is a second generation, reversible oral direct thrombin inhibitor, as dabigatran etexilate differs from dabigatran by the presence of an ethyl group at the carboxylic acid and a hexyloxy carbonyl side chain at the amidine. (51) After oral administration, dabigatran etexilate mesylate is converted to dabigatran. (2) The half-life of the drug is 12–17 hours. (2) The binding of dabigatran with the plasma proteins is low (almost 35%). (52) Metabolism starts in the gastrointestinal tract and finishes in the liver, but it is not affected by cytochrome P450, however as it is a substrate for the P-glycoprotein efflux pump, it is affected by P-glycoprotein inhibitors like ketoconazole. (2, 52) 80% of dabigatran is excreted by the kidneys, and for that reason renal impairment results in prolonged drug clearance and increased half-life. (2, 52) Dabigatran needs to be administered twice daily because after 4-6 hours the maximum concentration is reduced by approximately 30%. (52)

1.4.3.2. Apixaban

Apixaban is a highly selective and potent inhibitor of factor Xa. (51) Apixaban has an oral bioavailability of 50% and prolonged absorption, resulting in a half-life of 12 hours (10 to 14 hours) with repeat dosing. (2, 53) It is absorbed through the gastrointestinal tract, and its plasma peak is reached after two hours. (52) Apixaban is metabolized through the liver with a mechanism that is dependent on cytochrome P3A4. (52) Furthermore, it is a substrate of the cytochrome P450 and P-glycoprotein systems, and so drugs inhibiting both CYP3A4 and P-glycoprotein, and the impairment of renal or hepatic function, result in increased drug effect. (2) Excretion is mainly throughout the biliary system (75%), with only 25% via renal excretion. (52)

1.4.3.3. Rivaroxaban

This was the first selective oral direct factor Xa inhibitor that advanced to phase 3 clinical trials. (51) Rivaroxaban has a high oral bioavailability when taken with food and the peak plasma level is achieved within 2–4 hours. The drug is extensively protein-bound. (2) The drug half-life is 5–9 hours in patients aged 20–45 years, while in the elderly and in those with impaired renal or hepatic function this is increased. (2) The metabolism of rivaroxaban occurs in the liver through
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a mechanism that is independent of cytochrome P450 but dependent on cytochrome P3A4, whereas it is a substrate for the cytochrome P450 system and the P-glycoprotein transporter, so the drugs that inhibit both CYP3A4 and P-glycoprotein (e.g., ketoconazole) lead to an increased rivaroxaban effect. (2, 52) 33% of the active drug is excreted via the kidneys, while 66% is excreted through the faecal-biliary system with the interaction with P-glycoprotein. (2)

1.4.3.4. Edoxaban

Edoxaban has 62% oral bioavailability with peak drug concentrations occurring 1–2 hours after dosage, and the drug half-life is 10–14 hours. (2) Around 65% of the edoxaban is metabolized by the biliary-faecal system and it does not induce CYP450 enzymes. (2, 52) Approximately one-third of edoxaban is excreted unchanged via renal excretion. (2, 52) Also, it is a substrate for P-glycoprotein and cytochrome P3A4 like the other Xa factor inhibitors, and inhibition or induction of this pathway may alter plasma concentrations. (25, 52)

1.4.4. DOAC indications

DOACs have been specified for four main clinical settings: apixaban, dabigatran, edoxaban, and rivaroxaban for stroke prevention in patients with nonvalvular atrial fibrillation or flutter, treatment of venous thromboembolism, and also for prevention of venous thromboembolism after hip or knee replacement surgery (except for edoxaban which is licensed for this indication only in Japan). (54) Betrixaban has been licensed for prevention of venous thromboembolism in medically ill patients only in the USA. (54)

1.4.5. DOAC adverse effects

The major adverse effect of DOACs is bleeding, (25) and as with other anticoagulants, the risk of bleeding should be balanced with the probable benefit from the treatment. (48) According to a meta-analysis of phase 3 randomized controlled trials, when DOACs were compared to VKAs it was found that treatment with a DOAC is associated with a considerable reduction in the risk of major bleeding, intracranial bleeding, fatal, and clinically relevant non-major bleeding. (45) Bleeding stemming from DOACs can be classified as major bleeding (for example, central nervous system bleeding, hematemesis and melena) and non-major bleeding (including epistaxis, gingival bleeding, and some vaginal bleeding). (48)

1.4.6. DOAC drug interactions

There are relatively few drug-drug interactions between DOACs and other drugs compared with warfarin. (36) Dabigatran has fewer drug interactions than the three newer agents: Due to the
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fact that its metabolism does not involve the cytochrome p450 system (CYP), it is not inhibited or induced by many other drugs, and does not inhibit or induce the metabolism of other agents. (55) Apixaban and rivaroxaban interact with drugs that interact with P-glycoprotein and cytochrome P3A4. It has been contended that the drug interactions between inducers of P-glycoprotein and CYP3A4 and rivaroxaban or apixaban may be of greater clinical significance than interactions with inhibitors of P-glycoprotein or CYP3A4 as an increase in the risk of thrombotic events would potentially be more visible and more clinically significant than the minor increase in the risk of bleeding. (52, 56) Edoxaban is contraindicated with potent inhibitors of P-glycoprotein, for example the macrolide antibiotics (erythromycin, azithromycin and clarithromycin),azole antifungals, and HIV protease inhibitors, but limited data are available about the interaction between edoxaban and inducers of P-glycoprotein. (56) Furthermore, drug interactions with compounds that induce or inhibit CYP3A4 or other P450 enzymes were not an issue with edoxaban due to less than 4% being metabolised by the CYP system. (56) Unlike VKAs, which interact with various types of food, especially food products that contain vitamin K, the DOACs do not interact with food. (36, 52)

1.4.7. DOAC monitoring

DOACs have predictable pharmacokinetic and pharmacodynamic properties allowing the administration of fixed doses without the necessity for routine monitoring, unlike VKAs. (7, 57) The lack of a reliable procedure or a clear marker of anticoagulant activity of DOACs makes it very hard to ensure compliance. (7) Also in some circumstances, physicians may want to test either drug concentrations or a surrogate marker for drug levels that results from the use of DOACs - for example, in case of emergency situations such as a serious bleed and thrombotic events, the need for urgent surgery, or in special clinical conditions such as patients who present with renal or hepatic insufficiency, in cases of potential drug-drug interactions or of suspected overdosing, in cases of evaluating compliance or when choosing appropriate doses. (7, 49, 55, 57) There are a few assays like PT and aPTT that can be done quickly, and commonly utilized in emergency conditions, but they are not wholly reliable (57), while the tests that are reliable are time-consuming or barely available in institutions, not being widely commercially available. Also, they are of little use in emergency conditions. (48, 57) These assays include HEMOCLOT direct thrombin inhibitors assay (HYPHEN BioMed, France, CK002K) which is the recommended confirmatory test for drug levels of dabigatran, and drug-specific anti-factor Xa assays are recommended for apixaban, edoxaban, and rivaroxaban for confirmation. (48)
1.4.8. DOAC reversal agents (antidotes)

Initially, the primary barrier to more widespread acceptance of DOACs was the lack of a specific antidote to reverse the anticoagulant effects in case of trauma, severe bleeding, or the need for emergency surgery or other therapies (57), and this was considered one of the disadvantages and limitations in the use of DOACs according to several studies. (34, 47, 48, 51, 54, 57-59). However, by now three specific DOAC reversal agents have been developed (one agent is available on the market (idarucizumab) and two (andexanet alfa, ciraparantag) are in clinical development. (54, 60) Idarucizamab has been approved from the FDA for the reversal of dabigatran, while there are promising antidotes for oral factor Xa inhibitors; andexanet alfa (undergoing phase 3b to 4 trials), which reverses apixaban, betrixaban, edoxaban, and rivaroxaban, also heparins, and ciraparantag (undergoing phase II trials) acts as a potential universal antidote, which reverses all antithrombotics including all DOACs and heparins. (54, 57, 61, 62) In addition, there are non-specific reversal agents for DOACs: prothrombin complex concentrate (PCC), active prothrombin complex concentrate (aPCC), fresh frozen plasma (FFP), and activated charcoal. (57)

1.4.9. DOAC advantages and disadvantages

When comparing DOACs to warfarin, DOACs have numerous advantages; they facilitate long-term anticoagulation therapy due to the fact they do not need frequent INR monitoring and need less frequent dose adjustments (fixed dose). (34, 36, 47, 50, 57) Also, as previously mentioned they have a wide therapeutic window and considerably fewer drug and food interactions. (35) In addition, DOACs have predictable pharmacokinetics and pharmacodynamics, a rapid onset and offset of action, their short half-life allows patients to be fully anticoagulated the first day after starting DOACs, and this helps avoid the need to bridge with intravenous heparin or a heparinoid. (36, 57) However, these drugs are not ideal because their use is restricted or contraindicated under some conditions, for example owing to their higher cost, limited experience with these drugs, and lack of a reliable, rapid assay to measure their anticoagulant effect. (36, 57) Furthermore, they should not be used in patients with severe renal and hepatic disease because of the absence of a validated monitoring test, patients with mechanical heart valves, individuals younger than 18 years of age, and elderly patients. (36, 57) See Table 1.3 which shows the comparative pharmacokinetics and pharmacodynamics between DOACs and warfarin.
1. Introduction

*Table 1.3: Comparative pharmacokinetics and pharmacodynamics of oral anticoagulants, adopted from Nutescu et al., 2016. (25)*

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>Dabigatran</th>
<th>Apixaban</th>
<th>Rivaroxaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target(s)</strong></td>
<td>IIa, VIIa, IXa, Xa</td>
<td>IIa</td>
<td>Xa</td>
<td>Xa</td>
<td>Xa</td>
</tr>
<tr>
<td><strong>Prodrug</strong></td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Bioavailability (%)</strong></td>
<td>80–100 (pH dependent)</td>
<td>6.5</td>
<td>50</td>
<td>80</td>
<td>60</td>
</tr>
<tr>
<td><strong>Volume of distribution (L)</strong></td>
<td>10</td>
<td>50–70</td>
<td>23</td>
<td>50</td>
<td>&gt;300</td>
</tr>
<tr>
<td><strong>Peak effect</strong></td>
<td>4–5 days</td>
<td>1.5–3 h</td>
<td>1–3 h</td>
<td>2–4 h</td>
<td>1–2h</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>40h</td>
<td>12–17 h</td>
<td>9–14 h</td>
<td>5–9 h</td>
<td>10–14 h</td>
</tr>
<tr>
<td><strong>Renal elimination</strong></td>
<td>None</td>
<td>80 %</td>
<td>25%</td>
<td>33 %</td>
<td>35–50%</td>
</tr>
<tr>
<td><strong>Protein binding (%)</strong></td>
<td>&gt; 99</td>
<td>35</td>
<td>87</td>
<td>90</td>
<td>55</td>
</tr>
<tr>
<td><strong>Dialyzable</strong></td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Possible</td>
</tr>
<tr>
<td><strong>Interactions</strong></td>
<td>Many</td>
<td>P-gp*</td>
<td>3A4, P-gp*</td>
<td>3A4, P-gp*</td>
<td>3A4, P-gp*</td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>NO</td>
</tr>
<tr>
<td><strong>Antidote</strong></td>
<td>Vitamin K</td>
<td>Idarucizumab</td>
<td>No</td>
<td>No</td>
<td>NO</td>
</tr>
<tr>
<td><strong>Lab measure</strong></td>
<td>INR*</td>
<td>aPTT, TT, ECT*</td>
<td>Anti-Xa</td>
<td>PT, Anti-Xa</td>
<td>Anti-Xa</td>
</tr>
</tbody>
</table>

* P-gp: P-glycoprotein, 3A4: cytochrome P450 3A4, INR: international normalized ratio, PT: prothrombin time, aPTT: activated partial thromboplastin time, TT: thrombin time, ECT: ecarin clotting time
1. Introduction

1.5. PATIENT EDUCATION AND WARFARIN

Patient education has been defined by Van de Borne as “a systematic experience in which a combination of methods is generally used, such as the provision of information and advice and behaviour modification techniques, which influences the way the patient experiences his illness and/or his knowledge and health behaviour, aimed at improving or maintaining or learning to cope with a condition, usually a chronic one”. (63) Moreover, patient education relates to all educational activities directed at patients, involving aspects of therapeutic education, health education and clinical health promotion. (64) Patient education is not just about providing information, or interventions like counselling or behavioural instruction. (65) Patient learning of knowledge is frequently the main component in patient education, but it should not be limited to this alone. (65) Patient education may also affect emotions and attitudes and frequently aims to change the patients' behaviour. (63) Patients require simple information that is easy to understand in order to manage their self-care behaviour, so many strategies are required to ensure comprehension like utilizing easy-to-read patient education materials or those that do not require reading ability (e.g., videos, illustrations, cassette recordings). (66)

1.5.1. Health literacy

The term “health literacy” has been defined, refined, and measured in different ways over the years. (67) The World Health Organization (WHO) in 1998 defined health literacy as “the cognitive and social skills which determine the motivation and ability of individuals to gain access to, understand and use information in ways which promote and maintain good health”. (68) In one commentary study in 2010, the authors review the definitions of health literacy and in consultation with an expert panel, they added some suggestions for minor modifications to the health literacy definition, which was modified to be “The degree to which individuals can obtain, process, understand, and communicate about health-related information needed to make informed health decisions”. (67) Two review studies found that low health literacy was associated with poor health-related knowledge and comprehension, (69) and several adverse health outcomes. (70)

Hence it is essential to educate patients about the risks and benefits of anticoagulation, ensure that they understand how to take their oral anticoagulants (warfarin and DOACs), realize that anticoagulants can interact with other medications, and understand the importance of regular monitoring. (71)
1. Introduction

1.5.2. Patient education types

Patient education may include one or more of three main components: information only, counselling and behavioural treatment. (72-74) It forms part of the treatment program in daily practice and is rarely used as a single intervention. (74, 75) The first type, information only, involves all interventions aimed mainly at the interchange of information by way of convincing communication or informational brochures. Such interventions do not include any behavioural component and are not aimed at generating support. (72-74) Examples of the information patients need may include information to understand what is wrong, gain a realistic idea of prognosis, make the most of consultations, understand the processes and likely outcomes of possible tests and treatments, assist in self-care, learn about available services and sources of help, provide reassurance and help to cope, help others understand, legitimise seeking help and their concerns, learn how to prevent further illness, identify further information and self-help groups, or identify the “best” healthcare providers. (74, 76) The second type, counselling, includes interventions mainly aimed at social support and giving patients the chance to discuss their problems. (72-74) The third type of patient education, behavioural treatment, includes interventions that have techniques aimed at behavioural change, such as behavioural instruction, skills training, and biofeedback. (72-74)

1.5.3. Patient education methods

Patient education methods may broadly be considered to consist of traditional patient education methods (e.g. paper-based education methods: booklets, brochures, leaflets, and pamphlets), videotape, audiotape, one-on-one, teaching group and face-to-face counselling) and electronic/technology-based patient education (e.g. web-based patient education, interactive games, and interactive computer-based patient education).

1.5.3.1. Traditional patient education methods

Printed educational materials like booklets or brochures have the advantage that the patient can read the information many times, but they are often costly to produce, reorder and update, not suitable for illiterate patients, and may be very general and unspecific. (77-79) Compared to face-to-face counselling, one-on-one and teaching in groups, standard information materials like handouts, brochures, books and videos can reduce the variance in the healthcare education delivered and decrease the time that healthcare providers need to educate the patient. (78) Furthermore, the written information is presented at a constant reading age, in contrast to oral information which can be modified to ensure patient comprehension. (80)
1. Introduction

Face-to-face counselling is the most interactive way of educating patients because educators can use verbal and non-verbal communication techniques, but the patients may forget most of the information they received during the consultation. (79) Moreover, one-on-one and group teaching require space, resources, and a considerable amount of professional time and teaching expertise. (78) Also, the care-giver may not always recognize that the patient needs more clarification and this may result in miscommunication or misunderstanding. (78)

1.5.3.2. Electronic/technology-based patient education methods

Electronic education has many advantages: For example, patients can use it in the privacy of their own home at a convenient time, it is generally easy to use, exhibiting photographs and video clips does not need additional expensive hardware, and good quality programs containing text and graphics can thus be inexpensive. (77) However, compared to face-to-face counselling, the patient cannot ask direct questions and to date the information has been less likely to be tailored to the patient.

Visual aids have been found to improve medical assessment and education especially for patients with whom it is hard to communicate, (81) patients who experience difficulty learning from written materials, illiterate or low-level readers, those who have English as a second language, and those with visual and audio impairments. (78) These patients who find it hard to learn from traditional methods can get better education by getting the benefit of the multimedia features given by computer-based education, including self-paced learning and review, information print-outs, interactive graphics and animations, and closed captioning and narration. (78)

Further advantages of using technology for patient education, for instance, utilizing tablet-PCs which have user-friendly interfaces and large screens, have been found to improve simplicity and to be easy to handle even by chronically ill or elderly patients. (82)
1. Introduction

1.6. ADHERENCE

Adherence to medication is generally defined as the extent to which patients continue to take their prescribed medications, and do so as prescribed by their health care providers. (83, 84) The word compliance has also been used and defined as “the extent to which the patients’ behavior (including medication-taking) corresponds with medical or healthcare advice. (85) The negative connotations of this word regarding the patients’ behavior carry a risk of damaging the future relationship between these patients and their health care providers when they do not consume every pill at the desired time. (83, 85) Hence a majority of participants (60%) in the 13th Annual ESPACOMP meeting in September 2009 at Bangor University, Wales, UK, at which the ABC consortium coordinated the ‘European consensus meeting on the taxonomy and terminology of patient compliance’ agreed to use the “adherence to medication” term while only 25% voted for the term “Patient compliance”. (86)

1.6.1. The medication non-adherence classification:

Medication non-adherence can be classified as primary or secondary non-adherence, where primary non-adherence refers to when patients do not refill their prescription or even initiate a new prescription, while secondary non-adherence refers to when patients fill their prescriptions, but the medication is not taken as prescribed. (85, 87)

1.6.2. Adherence barriers:

The major barriers to adherence to medication are related to patients, medication, and health care providers, with common barriers being under the control of patients. (83, 88) Non-adherence to medication due to patient barriers includes two main categories: (a) knowledge about prescribed therapy and (b) motivation to change behavior, where health literacy and medication knowledge affect the patient’s ability to accommodate the knowledge about therapy, and the motivation and social support affect the patient’s ability to perform the plan. (88)

1.6.3. The measure of adherence

Adherence measurement can be classified as subjective or objective measurement according to the WHO; however most studies used the classification direct and indirect according to a study by Osterberg et al. (83-85, 89) Direct methods of measurement include directly observed therapy, the measurement of the level of drug or its metabolite in body fluids such as blood or urine, or measurement of a biological marker in blood, whereas indirect methods of adherence measurement include patient questionnaires and scales, self-reports, pill counts, rate of
prescription refills, assessment of the patient’s clinical response, assessing children’s adherence by using a questionnaire for their parents, school nurses, or teachers, electronic medication monitors, measurement of physiological markers (e.g., heart rate in patients taking beta-blockers), and patient diaries. (83-85)

1.6.3.1. Advantages and disadvantages of methods of adherence

Direct and indirect methods both have advantages and disadvantages; the direct methods are generally considered most accurate and can be used as physical evidence to prove that the patient has taken their medication, but they may be costly and difficult to perform because they may require many technicians and professionals to monitor the process and perform the tests. (85) Also, in the case of using direct observation as an example, patients can hide their medicines under the tongue and discard them afterwards, making routine inspection impractical. (85) Moreover, direct methods may be unsuitable for psychiatric patients and those under multidrug regimes. (85) On the other hand, indirect methods may be easy to use and inexpensive. (83) However, questioning the patient may be liable to misrepresentation, and this may lead to healthcare providers overestimating the patients’ adherence. (83)

1.6.3.2. Self-report measures

The most common measures of indirect methods used were self-report measures, pill counts, and pharmacy refills. (84) Electronic pill bottle monitors, pill counts, and pharmacy refill records (objective adherence measures) are generally considered more accurate than self-report measures (subjective adherence measures) which may be susceptible to many biases. (90) These objective adherence measures were impractical in most clinical settings, (90) whereas the prevalent use of self-report adherence measures in clinical care and health research reflects their low cost and the ease with which they may be carried out across a large variety of medication regimens. (91) Furthermore, the self-report measures’ advantages include noninvasiveness, minimal patient burden, and flexibility in timing and mode of administration. (91) There are three main types of self-report adherence measures in use; patient-kept diaries, patient interviews, and questionnaires and scales. (85, 92)

The 8-item Morisky Medication Adherence Scale (MMAS)

There are many types of self-report questionnaires and scales, for example; the Medication Adherence Questionnaire (MAQ), the 8-item Morisky Medication Adherence Scale (MMAS), and the Brief Medication Questionnaire. (85) In this thesis, the 8-item Morisky Medication Adherence scale was used because it is a validated questionnaire that is commonly used,
1. Introduction

relatively simple, practical to use in clinical settings, and most importantly has been shown to be predictive of the adherence to cardiovascular medications and blood pressure control. (84, 93) The original Morisky Medication Adherence Scale (MMAS) was developed in 1986 by Morisky et al. and comprised 4 items; however the authors developed the measurement scale to include 8 items in 2008 (see appendix 1). (93, 94) The type of questions in this scale are closed ended question style (yes/no). This adherence scale (MMAS) was developed to reflect the patient-drug errors of omission which may occur in any or all of several ways; when patients forget to take medicine, do not care about taking medicine, stop taking medication when feeling better or start it when feeling worse. (94) The 8-item Morisky Medication Adherence Scale (MMAS) has been translated into different languages. For example, two studies translated it to a Chinese version (Yan et al. and Wang et al.) (95, 96), and other versions include Malaysian by Al-Qazaz et al. (97), Brazilian–Portuguese by de Oliveira-Filho et al. (98), and Urdu by Saleem et al. (99).
1. Introduction

1.8. ORAL ANTICOAGULANT KNOWLEDGE TESTS

There are two main validated tests for oral anticoagulant knowledge: the anticoagulant knowledge assessment (AKA) test and oral anticoagulant knowledge (OAK) test. (100, 101) The AKA was developed and validated in 2005, USA by Briggs et al. and the OAK test was developed and validated in 2006, USA by Zeolla et al. (102, 103) Both tests are suitable for 7th grade (i.e. age 12-13 years) reading level based on Microsoft Word XP readability statistics and Flesch-Kincaid analysis, respectively. (102, 103) Material with a 7th grade reading level is considered to be of average difficulty according to the United States Department of Health and Human Services (USDHHS). (104) However, the authors of the AKA instrument believed that its effective reading level was less than 7th grade as if they removed the words "Coumadin" and “warfarin” from the instrument, the readability statistics showed a reading level of 5.5, and the result of their participants demonstrated that the items of the AKA test were understood, indicating the instrument performed well. (102) Similarly, for the OAK test the words "Coumadin" and "warfarin" repeatedly through the items may increase the reading level. (103) The reason for this inflates in the reading level because these clinically specific words (coumadin, and warfarin) are polysyllabic terms. (102)

1.8.1. Anticoagulant knowledge assessment (AKA)

The AKA test is a validated instrument that is designed to measure patients' knowledge. (100, 102) In this context, ‘validated instrument’ means that the test was entirely assessed for validity, question difficulty, readability, and reliability. (100) The authors chose to use multiple choice format questions, then they analyzed data from a sample of 60 patients using Rasch analysis, with a view to developing a tool that would score patients’ knowledge on an interval scale, hence allowing objective measurement of the effects of pharmacists’ educational interventions. (102) The tool comprises 29 questions and covers nine major educational topics. (See appendix 2.) The authors initially did a pilot study for the AKA instrument with 31 items covering ten major educational content areas (medication, medication administration, medication interactions, activity, diet, side effects, pregnancy, informing health care providers, procedures, and laboratory monitoring). (102) Stemming from the Rasch model results, the authors deleted two items that related to pregnancy due to these items not meeting the unidimensional requirements, so the final version of the AKA instrument contains 29 items with different levels of difficulty. (102) The unidimensional requirements in Rasch model mean “that all items forming the questionnaire measure only a single construct i.e. the latent trait under study, and
1. Introduction

local independence, which requires that, conditional to the latent trait, the response to a given item is independent from the responses to the other items in the questionnaire“. (105)

Many studies have measured their patients’ knowledge on oral anticoagulants or warfarin by using the AKA questionnaire. (81, 106-109) These studies translated the AKA test to different languages: Chinese (107), Danish (81), Persian (108), and modified to English UK instead of English US (106), and these trials were located in the hospital setting (81, 106-109). Ryals et al. set a standard for the passing score in 2011, whereby patients should answer at least 21 questions correctly. Scaling this up to a 100-point percentage scale (with each item worth 3.45 points), means that a score of 72.4% (passing score) or more indicates adequate knowledge of oral anticoagulants. (100)

1.8.2. Oral anticoagulant knowledge (OAK) test

The OAK test consists of a 20-item questionnaire with multiple choice format questions. (103) The OAK test covers five topics: basic drug information, adverse effects, drug-drug interactions, dietary issues/food interactions, and monitoring. (103) Many studies have assessed their patients’ knowledge of warfarin by using the OAK test in the hospital setting. (110-114) The OAK test tool has been translated to different languages, e.g. Arabic language by Elbur et al. (Saudi study) (113) and Khudair et al. (Qatari study) (111), and to the Malay language by Matalqah et al. (Malaysian study) (115). The Khudair et al. study used only 10 items of the OAK test, in which the questions covered drug interactions, vitamin K and diet, INR interpretation, action in case of a missing dose and its management, as well as when the patient should seek the emergency room. (111) A further study by Shibayeh et al. adopted the shorter knowledge test of Khudair et al. and undertook further assessment of its validity in conjunction with an adherence tool. (116) In the study of Elbur et al., they translated the test in collaboration with the English language centre in Taif University using the method of forward-backward translation, and they deleted three of the original 20 questions in the OAK test due to either cultural reasons or because they were considered to be too difficult for patients, so the total number of questions in the modified OAK test in this study became 17. (113) Matalqah et al. translated the OAK test using the forward-backwards translation methodology too; the forward translation was done by two qualified, independent linguistic translators who were native speakers of Malaysian and professional in English and the backward translation was accomplished by another translator with the final version created in a meeting to achieve unanimity. (115)
1.9. AIMS AND OBJECTIVES

1.9.1. Study aims

The aims of this study were to:

- Conduct a systematic review of technology-based education programs for warfarin patients.
- Design and evaluate in pilot studies new educational programs for oral anticoagulant (warfarin and DOAC) patients.

1.9.2. Objectives

In more detail, the objectives of this study were to:

- Identify and evaluate research on electronic educational methods for warfarin patients to provide a contemporary review of the evidence base.
- Develop and trial new oral anticoagulant educational programs for warfarin and DOACs using technology that gives flexibility to the patient to learn about his/her medication from any device at any time.
- Prepare an electronic format of the Morisky scale to measure baseline adherence for anticoagulant patients.
- Gather feedback from pilot studies utilizing the new tools, in order to refine them where necessary.
- Evaluate the patients’ oral anticoagulant (warfarin and DOAC) knowledge to explore the initial (short-term) impact of the educational programs.
1. Introduction
2. The Effects of Technology-based Educational Interventions for Warfarin: Systematic Review

2.1. BACKGROUND

2.1.1. Description of the condition

The most widely prescribed oral anticoagulant (OAC) in the world is warfarin. (10, 117) For many years, warfarin was the only OAC medicine commonly obtainable (118) and with an increasing number of patients receiving anticoagulant therapy, even though the new generation of oral anticoagulants (DOACs) are available, warfarin persists as the main therapy for many patients (119), still representing almost half of OAC prescriptions despite recent significant growth in the direct acting oral anticoagulants’ market share. (119)

Warfarin has many precautions for its use as it has a narrow therapeutic index which necessitates monitoring and follow up. (118) Also, it has many potentially serious interactions such as drug-drug, drug-food, and drug-alcohol interactions. (118) For a decade around the turn of the century, warfarin ranked number 9 in the United States among the primary suspect drugs having severe outcomes, i.e. death, hospitalization, life-threatening disability, congenital anomaly, and intervention required, and bleeding from warfarin use is a common result and a significant cause of mortality. (120) As a consequence the FDA requested warfarin producing companies to add a label (‘black box’) on warfarin products as a warning for the risk of bleeding, because of the increasing number of warfarin patients which was associated with an increase in the number of severe bleeding cases. (120) Furthermore, based on a large cohort study of older patients with atrial fibrillation, they found that the rate of haemorrhage was highest during the first 30 days after the patients started on warfarin therapy, and about 1 in 5 of the patients who had a haemorrhage and needed admission to hospital died either in hospital or shortly after discharge. (121) This highlights the importance of counselling patients to improve their knowledge of how to use warfarin, the possible side effects, the most critical drug interactions, action in case of missing a dose or emergency, and the risks associated with overdose and underdose, as this knowledge plays a vital role in achieving the desired clinical outcomes and decreasing adverse effects. (109)
2. Systematic review

2.1.2. Description of the intervention

Until approximately 10 years ago, patients were educated either by face-to-face counselling methods or by paper-based flyers and brochures. (79) A recent review found that the use of video-based technology in hospitals is prevalent for several medicine classes and while the effectiveness of these video-based education interventions depends on factors like presentation format, timing, and the emotional well-being of the target population, using electronic education played a substantial role in improving patients’ knowledge. (122) There are several possible forms that electronic counselling interventions may take, including animations, videos (e.g. of patients or healthcare professionals), narrated presentations, game-based activities or combinations of these. While these interventions may be delivered via desktop or laptop computers, the increasing availability and use of mobile technology is a more significant driver for their use: Data analysed in 2015 showed that 52.7% of the global population accessed the internet from their mobile phone and this percentage is expected to increase every year to reach 63.4% in 2019. (123) Also, data from 2015 indicate the percentage of internet users who use health and fitness apps every month increased to 15%. (124) These statistics illustrate that there is a high level of access to smartphones and good acceptability of their use for health purposes, and this provides a new way of delivering medication information to patients.

2.1.3. How the intervention might work

Previous investigation of warfarin patients’ knowledge indicates that an effective education program may need to be repeated periodically and areas of particular educational need include drug interactions with non-prescription drugs, dietary advice and recognition of emergency situations. (125) A systematic review of education strategies for warfarin patients determined that educational programs should focus on topics related to patient safety with oral anticoagulants rather than small details of anticoagulation that overburden the patient. (101) Also, they summarized the categories suggested by the studies included in the review (i.e. basics of anticoagulation, complications, adherence, accessing healthcare professionals in case of questions or emergency, diet, lab monitoring, medication interactions, self-care, self-testing). (101)

Electronic counselling provides a means of delivering a consistent set of information to patients. Depending on its design, knowledge checks and progress tracking may be included, some customization for individual patients may be possible, and the patient may be able to develop, refresh and reinforce their knowledge through ongoing access to the counselling program when healthcare staff are not present. This means patients may spend less time asking about things
that are not related to their health situation, also less face to face time may be needed to discuss confusing medical recommendations and theories that frustrate both patients and their healthcare providers. (126) So, utilization of online health education (OHE) has the potential to save time explaining treatment to patients compared with those who obtain information directly from their physicians or pharmacists only. (126) On the other hand, electronic counselling may not always include all these features. If electronic counselling were found to be an acceptable, effective and safe substitute for aspects of conventional patient counselling, the time spent by pharmacists and other healthcare professionals directly counselling patients could potentially be reduced, freeing them for other activities – including potentially more targeted face to face counselling of their warfarin patients following preliminary electronic education.

2.1.4. Why it is important to do this review

Warfarin has a narrow therapeutic window, so it is critical to educate patients about the risks and benefits of anticoagulation and ensure that they understand how to take warfarin, ensure they recognize the other medications that interact with warfarin and that they know the importance of regular monitoring. (71) Systematic reviews have been conducted on the general types of educational interventions for oral anticoagulant therapy; for instance, one recent review was on the effect of educational interventions on TTR specifically in patients with AF (127), and an older (2008) review sought to identify the best patient education strategies and the best instruments for measuring patient knowledge. (101) However, to date no systematic reviews have focused explicitly on examining the effectiveness of electronic counselling interventions for warfarin patients. As advances in technology facilitate the development and use of electronic counselling, it is timely to examine the evidence of their impact from studies to date.
2. Systematic review

2.2. AIMS AND OBJECTIVES

2.2.1. Study aims

The aim of this study was to:

- Conduct a systematic review on electronic education counselling for warfarin patients.

2.2.2. Objectives

Specifically, the objectives of this study were to:

- Identify and evaluate research on technology-based education for warfarin patients to provide a contemporary review of the evidence base.
- Assess the effects of patient education delivered for warfarin patients compared with usual care on their knowledge of medication, and clinical outcomes.
2.3. METHODS

2.3.1. Criteria for considering studies for this review

2.3.1.1. Types of studies

Randomized controlled trials (RCTs), and quasi-randomized controlled trials in which patients were assigned to groups by methods other than true randomization (e.g. alternate assignment) were included. Inclusion was not restricted by publication type. All studies published in English that met our selection criteria were included. However, studies were excluded that did not have a control arm, or enough information to determine the effect of the intervention relative to the control.

2.3.1.2. Types of participants

Studies of patients on warfarin treatment were included, but studies which focused solely or primarily on interventions for healthcare professionals, services or systems were excluded.

Study selection was not restricted to a particular age group or type because the objective was to assess the effectiveness of digital educational interventions for all patients on warfarin. No restrictions were placed on the length of time for which the patient had taken warfarin (e.g. newly diagnosed or longstanding patients).

Programmes that also incorporated education for careers or relatives were included, provided the intervention was primarily intended for the patient taking warfarin.

2.3.1.3. Types of interventions

There are many potential interventions to influence the education of patients on warfarin. This review was open to the inclusion of patient interventions with a clear and distinct digital education component which were directed at any of the following, as they related to warfarin therapy:

- Facilitating communication and/or decision making by patients in connection with their anticoagulant treatment.
- Acquiring skills and competencies.
- Supporting behaviour change.
- Minimising risks or harm of adverse effects.
- Improving the quality of patients’ care.
2. Systematic review

- Patients’ system participation.
- Supporting technological education.

Education delivered to groups or individuals were considered.

No restrictions were placed on the required duration of the intervention or follow up.

No restrictions were placed on the educator (i.e. it did not necessarily need to be a pharmacist).

No restrictions were placed on the setting in which the intervention was conducted (primary care, secondary care etc.)

Excluded studies were those that were:

- Not a structured educational intervention. (For example, studies that relied solely on informal information provision without a structured format or some form of organized content delivery were excluded.)
- Educational programs focusing primarily on another topic, where education on warfarin formed only a small part of the program.
- Not a digital intervention.

2.3.1.4. Types of outcome measures

Immediate (up to four weeks from the start of the intervention), intermediate (from one month up to and including one year after the intervention) and longer-term outcomes (longer than one year after the intervention) were all eligible for consideration.

Primary outcomes

The main outcome of interest was the knowledge of patients about warfarin and its use.

Secondary outcomes

There are other types of outcome measures that are available to measure the impact of warfarin education which include adherence and behavioural change measures. Other secondary outcomes of interest included clinical outcomes such as INR range, and time in therapeutic range (TTR).
2. Systematic review

2.3.2. Search methods for identification of studies

2.3.2.1. Electronic searches

We identified studies through searching the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library.
- MEDLINE (Ovid).
- CINAHL Plus (EBSCOhost)
- Web of Science (Thomson Reuters).
- PubMed
- ERIC Pro Quest.

The literature search strategy is outlined below.

Table 2.1: Literature search strategy

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<td>Cochrane Library</td>
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<tr>
<td>Web of Science</td>
<td>See appendix 9.</td>
<td>1520</td>
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2.3.2.2. Searching other resources

We also searched for trials on the following:

- EU clinical trials (EudraCT).
- US clinical trials (clinicaltrials.gov).

Studies found from other resources such as manual searches of reference lists in relevant publications were also included.

2.3.3. Data collection and selection of studies

All identified references for inclusion based on our inclusion criteria were imported and sorted using Endnote software. Duplicated references were discarded automatically and refined
2. Systematic review

manually. The publications were then screened on the basis of their titles, abstracts and, where necessary, full texts, assessing them for eligibility and discarding the irrelevant studies.

2.3.3.1. Data extraction and management

Study characteristics were extracted from included studies in accordance with Cochrane Review Manager 5.3 (Rev Man 2014) procedures, namely:
1. Methods: study design, blinded, and total duration of study.
2. Participants: sample size, study setting, inclusion criteria, and exclusion criteria.
3. Interventions: intervention group (total number, type of intervention and brief information about the intervention), and control group (total number, and brief information about the control group).
4. Outcomes: primary and secondary outcomes specified and collected.

2.3.3.2. Assessment of risk of bias in included studies

The risk of bias of the included studies was determined according to the Cochrane Handbook for Systematic Reviews of Interventions. The risk of bias was assessed using the Cochrane ‘risk of bias’ tool taking into account the following criteria:

- Random sequence generation (selection bias).
- Allocation concealment (selection bias).
- Blinding of participants and personnel (performance bias)
- Incomplete outcome data (attrition bias).
- Selective reporting (reporting bias).
- Other sources of bias.

For each criterion, the risk of bias was graded as low risk, high risk, or unclear risk.

2.3.3.3. Measures of treatment effect

Prior to conducting the review, it was planned to pool the outcome data (for example, results of knowledge tests and the clinical outcomes such as time in therapeutic range) and analyse the dichotomous data as odds ratios and risk ratios with 95% confidence intervals like for pass/fail test scores. It was also hoped to calculate the continuous data as the mean difference or standardized mean difference with 95% confidence intervals, e.g. for changes in TTR and the difference in knowledge before and after the intervention and after the follow-up if applicable. However, owing to the heterogeneity of the outcome measures, study groups and the follow-
up interval used in studies identified, it was ultimately necessary to report the outcomes for each study without pooling. (See the effect of the intervention, section 2.4.3.)

2.3.3.4. Dealing with missing data

Study authors were contacted to ensure that the missing data from the study (when comparing it with previously published protocols) had not influenced the result, nor led to a significant bias.

2.3.3.5. Assessment of heterogeneity

Because of the small number of the included studies and the difference in their outcomes and outcomes measures, it was not possible to assess heterogeneity quantitatively, but by comparing the characteristics of included studies, a qualitative determination of heterogeneity was made for these studies.

2.3.3.6. Assessment of reporting biases

The outcomes of the included studies were quite complete except for one study where no response was received to enquiries directed at the author about the cost-analysis outcome. On the other hand, all the relevant trials identified were found to have subsequently been published. Outcomes are still awaited for one ongoing trial (NCT03125668 (128)).

2.3.3.7. Unit of analysis and data synthesis issues

A meta-analysis was not undertaken because of the heterogeneity of the included studies with regard to their interventions, participants, outcomes and outcome measures. Therefore, there were no unit of analysis issues, nor issues with data synthesis.

2.3.3.8. Sensitivity analysis

For similar reasons (insufficient studies) a sensitivity analysis was not undertaken.
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2.5. RESULTS

2.5.1. Description of studies

2.5.1.1. Results of the search

A total of 7374 records were identified through database searching and 872 trials through searching in the clinical trials registers, so the total number of records before de-duplication was 8246 references. After duplicates had been discarded the total became 3906 records (3035 records of databases and 871 trials). From this point, the records were screened and records were excluded according to the title (3690 records), abstract (183 records), one record was non-English, and two records were excluded on the basis of overlapping updated references. Subsequently, 30 articles were assessed as full-text for eligibility, 26 of which were excluded.

Overall, the final analysis reports three studies and one ongoing trial corresponding to our inclusion criteria. Details about each study and the risk of bias have been summarized in the ‘Characteristics of Included Studies’ tables: Table 2.3, Table 2.4, Table 2.5.

The PRISMA flow diagram includes detailed information about the total number of studies identified, de-duplication, numbers included and excluded, and reasons for exclusions in each step of screening. See Figure 2.1.

2.5.1.2. Included studies

Three studies have been included (Clarkesmith 2013 (129), Moore 2015 (130), Talboom-Kamp 2017 (131)) with a total of 384 participants who were taking warfarin medication and one ongoing trial (NCT03125668 (128)). See Table 2.10 for the study details. The three studies were randomized trials (parallel cohort design with two randomised self-management groups and usual care group (Talboom-Kamp 2017 (131)), randomised controlled trial (Clarkesmith 2013 (129)), and a prospective, randomized open, parallel-group study (Moore 2015 (130)). These trials compared education using video, group session with one hour shown a DVD containing information about OAC, and self-management plus education (e-learning and group training) to usual care, with follow-up ranging from seven days after the intervention to 18 months in the three trials (Clarkesmith 2013 (129), Moore 2015 (130), Talboom-Kamp 2017 (131)). The three studies recruited from; a specialist AF clinic or local anticoagulation outpatient clinic, Birmingham, United Kingdom (Clarkesmith 2013 (129)), four family practices and a geriatric day clinical program, University of North Carolina Medical Center (UNC MC) (Moore 2015 (130)), and Primary Care Thrombosis Service Center (Talboom-Kamp 2017 (131)).
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More information summarized about the features of the intervention and control groups and the outcomes are included in the ‘Characteristics of Included Studies’ tables; Table 2.3, Table 2.4, Table 2.5.

2.5.1.3. Excluded studies

26 studies which did not meet the inclusion criteria were excluded upon review of the full-text. Seven articles did not contain a control arm (four articles were pilot studies and three were pre-post interventions), three articles were not related to warfarin, three articles were not relevant to any technological education intervention, two studies were a survey, two articles were protocols, two studies were not RCTs, two were letters to the editor, two were systematic reviews, one study did not include specific results for warfarin patients, one study was not related to education, and one was an invited commentary for a meta-analysis study. See Table 2.9.
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![Prisma study flow diagram]

Figure 2.1: Prisma study flow diagram
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2.5.2. Risk of bias in included studies

According to the Cochrane ‘Risk of bias’ tool, we assessed the risk of bias of the included studies and judged them to be of low, high, or unclear risk. The results of this judgement are outlined in the ‘Risk of bias of included studies’ tables: Table 2.6, Table 2.7, Table 2.8.

2.5.2.1. Allocation (selection bias)

Three of the studies randomly allocated the participants by using adequate random sequence generation (Clarkesmith 2013 (129), Moore 2015 (130)). Therefore, we judged them as low risk. One study was judged as high-risk because the randomization was by three unsuitable methods (Talboom-Kamp 2017 (131)).

Allocation concealment was judged as low risk for the two studies (Clarkesmith 2013 (129), Moore 2015 (130)) due to including a researcher who was responsible for patient allocation and was not otherwise involved in the conduct of the study. On the other hand, one study was judged as high risk because they allowed the participants to choose the group to which they wished to be recruited (Talboom-Kamp 2017 (131)).

2.5.2.2. Blinding (performance bias and detection bias)

Due to the nature of these interventions, blinding of the participants was unlikely to be possible. Two studies (Moore 2015 (130), Talboom-Kamp 2017 (131)) were judged to have a high risk of bias because they clearly mentioned that the participants were not blinded. One study was judged to be of an unclear risk due to insufficient information (Clarkesmith 2013 (129)). As regards to the blinding of the outcome assessment, two studies (Clarkesmith 2013 (129), Moore 2015 (130)), reported adequate blinding, and were therefore judged to be at low risk of bias. The outcome assessment was not blinded in one study (Talboom-Kamp 2017 (131)) and they were judged to be at high risk of bias because the subjective outcomes may have been influenced.

2.5.2.3. Incomplete outcome data (attrition bias)

All the three studies (Clarkesmith 2013 (129), Moore 2015 (130), Talboom-Kamp 2017 (131)) were at high risk of bias as they clearly declared the numbers of participants who dropped out or were lost to follow-up.

2.5.2.4. Selective reporting (reporting bias)

The protocol was not available separately for one study (Moore 2015 (130). The study authors reported the protocol contemporaneously with the results as part of the methods, and this study
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was treated as being at high risk of bias. Otherwise, two studies were judged to be of low risk of bias (Clarkesmith 2013 (129), Talboom-Kamp 2017 (131)), for disseminating the protocol separately as when the outcomes mentioned in the study were compared with the outcomes reported in the protocol, it was found that they reported all the outcomes in an adequate way. A cost-analysis outcome was reported in the methods of these protocols which was not found in the study results. Therefore, the authors were contacted and for one of the studies (Talboom-Kamp 2017 (131)) a response was received indicating that analysis of this outcome was ongoing, but for the other study (Clarkesmith 2013 (129)) no response was received.

See Figure 2.2 and Figure 2.3 for risk of bias summary: review authors' judgements.

2.5.3. Effects of interventions

Because of the heterogeneity between the included studies concerning the study groups, methods and follow up periods, the results of outcomes and outcome measures were not pooled in a summary of findings table for the main comparison. Instead the results for each outcome have been described separately and in narrative form.

2.5.3.1. Knowledge of patients and comprehension

The three included studies (Clarkesmith 2013 (129), Moore 2015 (130), and Talboom-Kamp 2017 (131)) measured knowledge improvement in patients by using different electronic intervention and different knowledge measurement tools. Furthermore, the three studies assessed the knowledge of patients before and after the intervention with different follow-up intervals.

The (Clarkesmith 2013 (129)) study designed a DVD model which had information for patients about the OAC. The patients who were included in the study attended one group session consisting of 1-6 patients for four hours where the patients were encouraged to ask questions and complete a worksheet-based exercise following each 10 minute DVD section.

The (Moore 2015 (130)) trial used a video developed by UNCMC clinical pharmacists in collaboration with the UNC Eshelman School of Pharmacy, provided on a tablet device, for counselling in the intervention group. This video consisted of informational slides with a voiceover recording. The study of (Talboom-Kamp 2017 (131)) included two intervention groups, one of which used an online self-management portal called Portavita for e-learning, and the second of which attended group training courses carried out by specialized and expert healthcare professionals.
The **(Clarkesmith 2013 (129))** study assessed the knowledge of participants using the patients’ knowledge questionnaire with 14-items that were designed and piloted by the study researcher group. However, the **(Moore 2015 (130))** trial measured the patients’ knowledge using the previously validated OAK test comprising a 20-item multiple choice questionnaire. In the **(Talboom-Kamp 2017 (131))** study, the first module contained general education about the oral anticoagulants including test questions, and the patients could only pass the test after all questions were answered correctly, but details of the knowledge test were not provided.

The **(Clarkesmith 2013 (129))** study reported good levels of knowledge in both groups of patients at baseline. There was a slight increase in knowledge scores in the intervention group over time. Also, a significant improvement in knowledge was found across time with \( p<0.04 \), but not between the two groups. In contrast, the study of **(Moore 2015 (130))** reported that there were no significant differences in overall OAK test scores when the two counselling methods were compared (\( P = 0.406 \)): The mean scores after video and face-to-face counselling were 74.3% and 71.3%, respectively. Although the **(Talboom-Kamp 2017 (131))** study involved testing patients’ knowledge of oral anticoagulant information in the education section in the portal, they did not mention the outcome of the patients’ knowledge test in the study, focusing more on the clinical impact of the educational intervention.

### 2.5.3.2. Time in therapeutic range (TTR)

Two studies **(Clarkesmith 2013 (129), and Talboom-Kamp 2017 (131))** measured time in therapeutic range (TTR) with INR 2.0 to 3.0. Also, **(Talboom-Kamp 2017 (131))** reported the TTR with INR 2.0 to 3.5 and the sensitivity analysis showed no effect on the results. **(Clarkesmith 2013 (129))** reported the TTR in two groups (intervention group and usual care group) following 6 and 12 months of follow-up, while **(Talboom-Kamp 2017 (131))** reported the TTR using three groups (group1: e-learning, group 2: training, and group 3: usual care) over a time spanning 6 months before the intervention to 18 months afterwards. The TTR in both the **(Clarkesmith 2013 (129), and Talboom-Kamp 2017 (131))** trials was determined by using Rosendaal methods.

In the **(Clarkesmith 2013 (129))** trial, the TTR in the intervention group was significantly higher than the usual care group at six months (76.2% vs 71.3% respectively; with \( p= 0.035 \)), while there was no significant difference between the intervention group and usual care group at 12 months (76.0% vs 70.0 % with \( p= 0.44 \)).
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The TTR in the study of (Talboom-Kamp 2017 (131)) showed no significant differences over time between the three groups, nor did the two intervention groups (e-learning group and training group) show significant within-group differences in TTR over time.

2.5.3.3. Quality of life

The (Clarkesmith 2013 (129), and Talboom-Kamp 2017 (131)) studies reported the quality of life using different measurement tools. In the (Clarkesmith 2013 (129)) trial this was measured by the Atrial Fibrillation Quality of Life (QoL) questionnaire, an 18-item health-related QoL scale, whereas the (Talboom-Kamp 2017 (131)) used the EuroQol-5D (EQ-5D), a five-item questionnaire. In the (Clarkesmith 2013 (129)) study the intervention group was found to have a lower QoL score at the baseline (i.e. worse than the usual care group), but after one month follow up the intervention group showed an increase in the QoL scale. However, there were no significant differences in QoL scores between groups, and no significant differences in QoL scores between or within groups from the baseline to 12 months follow-up. Similarly, the (Talboom-Kamp 2017 (131)) study reported no significant differences between the three groups in EQ-5D with p< 0.036 (X^2_2=6.66).

2.5.3.4. Severe complications or adverse event

Two studies (Clarkesmith 2013 (129), and Talboom-Kamp 2017 (131)) reported on severe complications. The (Clarkesmith 2013 (129)) study identified only eight adverse events through the 12 month follow-up period; one in the intervention group (peripheral embolism), while seven occurred in the usual care group (three ischaemic, non-fatal strokes, two minor bleeding episodes, one major bleeding episodes, and one non-cardiac related death). For the (Talboom-Kamp 2017 (131)) study, during the 18-month period over all three groups after the intervention, the study reported three severe complications (3 of the total participants 247=1.2%); 2 of 63 total in the e-learning group had muscular bleeding, and one of 74 total patients in the training group had a cerebrovascular accident, with no complications reported in the usual care group.

2.5.3.5. Self-efficacy (Generalized Self-Efficacy Scale (GSES))

One study (Talboom-Kamp 2017 (131)) reported self-efficacy using GSES and found there was no association with TTR (P=0.717) over a 6 month period.
2.5.3.6. Usage of the platform

The (Talboom-Kamp 2017 (131)) study reported how many patients had logged onto the self-management portal (Portavita) during the 18-months since the patients started to use the platform, and they found no significant differences between the self-management groups (group 1 and group 2) during three intervals (from 0 to 6 months: SD=5.20, P=0.764; from 6 to 12 months: SD=7.0, P=0.866; and from 12 to 18 months: SD=7.39, P=0.260).

2.5.3.7. Beliefs about medication

One study (Clarksmith 2013 (129)) reported that there was a significant difference between the three groups in the perception of the general harm of medication with p<0.05, with the intervention groups having lower harm perceptions than the usual care group. There was no significant change across time in patients’ perception of general harm.

2.5.3.8. Illness perception

One study (Clarksmith 2013 (129)) reported on illness perception as they found a significant difference in patients’ perception of the timeline of AF across time with p<0.01, but no significant differences between groups. Patients in the intervention group scored higher on illness coherence, lower on emotional representation, and lower on illness concern than the usual care group.

2.5.3.9. Difference in pharmacist time spent counselling (total time) between the video and face-to-face counselling groups and total time including time for scripted counselling, teach-back questions, and follow-up questions

One trial (Moore 2015 (130)) reported that the mean total counselling time was significantly reduced in the video group (p<0.001). However, prior warfarin use was a significant factor (P = 0.006), and the researchers observed a significant interaction between prior warfarin use and counselling method (P = 0.012). As a result of that, comparisons between the two warfarin-use strata were made. The mean total time in restart participants was reduced in video counselling by 8.71 minutes when compared to the face-to-face counselling group with P<0.001. In new start participants who were in the video counselling group, the mean total time was reduced by 2.31 minutes (with adjusted p=0.472) which was not statistically significant.
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2.6. DISCUSSION

2.6.1. Summary of main results

In this review, we included only three randomized controlled trials (Clarkesmith 2013 (129), Moore 2015 (130), Talboom-Kamp 2017(131)) and one ongoing study (NCT03125668 (128)) was also identified with a small sample size. The three studies varied in length (from 0 to 18 months). Furthermore, these trials were too heterogeneous to conduct a meta-analysis.

The three studies had different types of electronic intervention designed with the aim of improvement in patients' knowledge of warfarin. Also, they measured knowledge with different questionnaire tools. See Table 2.2 below for more information about each study intervention type, intervention group, usual care group, knowledge test tool, and level of improvement.
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*Table 2.2: Comparison of the identified studies according to intervention type, intervention group, usual care group, knowledge test tool, and level of improvement.*

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention type</th>
<th>Intervention group</th>
<th>Usual care group</th>
<th>Knowledge test tools</th>
<th>Level of improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarkesmith 2013 (129)</td>
<td>TREAT intervention</td>
<td>One group session (between 1-6 patients) for one hour, during the session the patients shown a DVD containing information about the OAC</td>
<td>Standard yellow booklet including information on OAC.</td>
<td>Patients knowledge questionnaire with 14-items designed and piloted by the study researcher group</td>
<td>There was a significant improvement in knowledge across time but not between groups</td>
</tr>
<tr>
<td>Moore 2015 (130)</td>
<td>Video provided on a tablet device.</td>
<td>Video-counselling</td>
<td>Face-to-face counselling</td>
<td>OAK test</td>
<td>No significant differences in overall OAK test scores between the two counselling methods.</td>
</tr>
</tbody>
</table>
2. Systematic review

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention type</th>
<th>Intervention group</th>
<th>Usual care group</th>
<th>Knowledge test tools</th>
<th>Level of improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Talboom-Kamp 2017 (131)</td>
<td>Online self-management portal named Portavita</td>
<td>Group 1: e-learning</td>
<td>Group 3: basic training + written instructions by thrombosis doctor</td>
<td>did not report what types of tools they used to measure knowledge</td>
<td>No result reported. we contacted the author by email to ask him about the results and the tool and he answered with “All patients showed a significant improvement of their knowledge, exactly the same for the e-learning group as after the classical group training. We tested their knowledge on their disease, the anticoagulant therapy and self-management skills”.</td>
</tr>
</tbody>
</table>
From this table, it is evident that the included studies demonstrated different levels of knowledge improvement and the study which reported significant improvement was the (Clarkesmith 2013 (129)) study with the TREAT intervention. For the (Moore 2015 (130)) study with a video counselling intervention, a significant improvement in the OAK knowledge test was not found between the two groups, and they suggested that the nonsignificant nature of the OAK results in their study might be a result of the homogeneous study population and the small sample size. On the other hand, in the (Talboom-Kamp 2017 (131)) study with an online self-management portal intervention, the researchers did not report the types of knowledge tools they used in the study and the results of this test. However, when the author was contacted by email, he responded that there was a significant improvement in the patients’ knowledge.

Two studies (Clarkesmith 2013 (129), Talboom-Kamp 2017 (131)) reported time in therapeutic range as the primary outcome and quality of life as a secondary outcome. Both studies reported no significant differences on TTR between groups, also no significant differences on QoL between the groups.

The (Talboom-Kamp 2017 (131)) study reported severe complications as the primary outcome, whereas (Clarkesmith 2013 (129)) reported it as a secondary outcome. In addition, both studies reported several adverse events during their follow up. The (Clarkesmith 2013 (129)) study reported eight severe complications cases (one in the intervention group and seven in the usual care group), and in (Talboom-Kamp 2017 (131)) study reported three cases (two in the e-learning group and one in the training group), with no adverse events reported in the usual care group.

Each study had additional outcome measures; for example, the study conducted by (Talboom-Kamp 2017 (131)) reported on self-efficacy (Generalized Self-Efficacy Scale (GSES)) and the usage of the platform as secondary outcomes, they found that there was no association in Generalized Self-Efficacy Scale with TTR and there were no significant differences between self-management groups in the usage of the platform. The (Clarkesmith 2013 (129)) study reported on anxiety/depression, beliefs about medication, and illness perceptions as secondary outcomes. Regarding anxiety/depression, they reported significant differences in anxiety between the two groups, but no significant differences were reported in depression between the two groups. Regarding beliefs about medication, they found that the intervention group considered them less harmful than the usual care group. Finally, regarding the illness perceptions, the patients in the intervention group scored higher on illness coherence, lower on emotional representation, and lower on illness concern than the usual care group.
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The study conducted by (Moore 2015 (130)) was the only study to report on the difference in pharmacist time spent counselling (total time) between the video and face-to-face counselling groups, and they reported that the use of video counselling significantly reduced the pharmacists’ time required for anticoagulation counselling, especially in the restart group, but that there was non-significant reduction in the new start group. The reasons for this were unclear, and they indicate finding may be due to the small sample size or because this information was new to them, and that they need time to acquire the information.

2.6.2. Overall completeness and applicability of evidence

This review used a comprehensive search strategy, which followed Cochrane search methods, and was not restricted by publication status, although it was restricted to English language studies. Due to the challenges of conducting RCTs, this means that relatively few studies met the inclusion criteria, and hence only three RCT studies were included in the study.

A variety of interventions were studied, which had different strategies in the way of education. The (Moore 2015 (130)) study intervention concerned use of a prerecorded video provided on a tablet device, whereas the (Clarkesmith 2013 (129)) study was a group education session named TREAT that included use of a DVD providing information on OAC along with an educational booklet, self-monitoring diary and worksheet. In the (Talboom-Kamp 2017 (131)) study, the intervention was via an online self-management portal called Portavia. This application had a patient portal and a healthcare provider portal, in which the healthcare portal provides space for the OAT protocol, medication records and information about complications, while the Portavita anticoagulation self-management patient portal provides a diary tool for self-monitoring and self-dosage and education for patients and it also allows for personal notes for healthcare professionals to send advice and notes to the patient. Despite all these differences in the interventions’ types and methods, all reported improvements in the patients’ knowledge.

The evidence of this review is applicable to patients aged more than 18 years old taking warfarin therapy. These studies were mainly for warfarin patients, so the results are not applicable to other anticoagulants. The length of follow-up varied between trials, as two trials (Clarkesmith 2013 (129), Talboom-Kamp 2017 (131)) had a long-term follow-up of 12-18 months, while one trial (Moore 2015 (130)) had a short-term follow-up of seven days after the intervention. For this reason it is not possible to apply this finding to longer periods.
Furthermore, the evidence of this review is applicable to a range of different settings as with the (Clarkesmith 2013 (129)) study, the setting was a specialist AF clinic or local anticoagulation outpatient clinic, while the (Moore 2015 (130)) study was on the University of North Carolina Medical Center (UNCMC) which is an academic medical center, and the study of (Talboom-Kamp 2017 (131)) was in a Primary Care Thrombosis Service Center. However, no study was done in community pharmacy.

All of the three completed trials (Clarkesmith 2013 (129), Moore 2015 (130), and Talboom-Kamp 2017 (131)) took place in high-income countries (UK, USA, and the Netherlands respectively), whereas the ongoing study (NCT03125668 (128)) took place in an upper-middle income country (Brazil).

2.6.3. Quality of the evidence

All of the studies included in this review were randomized controlled trials, but we could not pool the data to assess the quality of evidence using the GRADE approach for evidence synthesis due to the fact that these identified studies were too heterogeneous in their outcomes and outcome measures. Also, it is important to note that the sample sizes of the included four trials were small (a total of 482 participants), and these small trials are more likely than larger trials to be insufficiently powered to detect clinically and statistically significant differences between groups. The sample size for all identified studies were calculated by different methods and the sample sizes actually attained were in line with the calculated required values. The study conducted by (Clarkesmith 2013 (129)), the sample size calculated for the primary outcome was based on data from a secondary analysis of TTR from the ACTIVE-W cohort by Connolly et al. (132) and the sample size was 156 participants (78 in each group), to allow for a 20% attrition rate. For the secondary outcome of improvement in knowledge following the intervention, the sample size was calculated based on a study by Khan et al. (133) and it was 100 patients (50 participants in each group), this allowed for a 20% attrition rate in the completion of the questionnaires, and at least 80% power to detect a 18.5% increase in knowledge about the condition and factors affecting INR control between baseline and follow-up. Regarding the study performed by (Moore 2015 (130)), the sample size was calculated as 19 participants per counselling group (38 participants total) were needed for the study power of 85% and 2-sided $\alpha$ of 0.05. Moreover, in the (Talboom-Kamp 2017 (131)) study, to detect a relevant effect of the new implementation strategy of e-learning or group training (>5%) at a power of 80% with $\alpha$ =0.05, the sample size was calculated as a requirement for 63 patients per group. Allowing for a 15% dropout this means 72 (63/0.85) patients were required per study group.
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Each study had at least two risks of bias judged as high risk. Two of the studies \cite{ClarkeSmith2013, Moore2015} provided details about the generation of a random sequence when assigning patients to the different study arms, and the appropriate concealment of allocation (selection bias) were judged at low risk, whereas due to the methods of randomization and no allocation concealment, the study of \cite{Talboom-Kamp2017} was at high risk of bias.

Moreover, because of the nature of the interventions, the majority of the studies \cite{Moore2015, Talboom-Kamp2017} were at high risk for performance bias as blinding was impossible. One study \cite{ClarkeSmith2013} was judged to be at unclear risk of performance bias due to insufficient details about the participants’ blinding. Two of the studies \cite{ClarkeSmith2013, Moore2015} were judged at low risk for detection bias and one study \cite{Talboom-Kamp2017} were judged to be at high risk of bias due to inadequate blinding.

In three studies \cite{ClarkeSmith2013, Moore2015, Talboom-Kamp2017} attrition was judged to be a high risk of bias. In terms of reporting bias, we judged three studies to be at high risk: In \cite{ClarkeSmith2013} study not all the measures outlined in the study protocol had been reported and no comment on this was obtainable from the author, and for \cite{Moore2015} it was part of the study methods. On the other hand, one study \cite{Talboom-Kamp2017} judged at low risk of bias due to the fact that all prespecified outcomes outlined in the protocol were described in the trial except for one outcome which the author indicated was still undergoing analysis in preparation for publication.

It is worth noting that the heterogeneity of the studies in this review not only has implications to the applicability of the evidence but also indicated that the quality of reporting for trials evaluating warfarin patients’ educational interventions is very poor.

2.6.4. Potential biases in the review process

The searching in this review was extensive involving a number of different databases, and we also looked for unpublished data, although we only found one unpublished randomized controlled trial in a clinical trial database that fulfilled our inclusion criteria; therefore, this review contains only published data and identifies one additional ongoing trial (unpublished).

This review is currently limited by the small number of the identified studies and the heterogeneity between studies regarding the intervention and participant characteristics, and length of follow-up, outcomes and outcome measures along with small sample sizes. As a result,
we did not conduct a meta-analysis study. In addition, Further studies are required to support the evidence and to be able to determine the effects of the interventions on clinical events. Furthermore, one Korean study was excluded because this study was a non-English resource, and this could lead to bias in this review.

2.6.5. Agreements and disagreements with other studies or reviews

This evidence is believed to be the first systematic review of electronic counselling for warfarin patients. Most previous reviews have had a broader focus, exploring multiple different education methods including traditional (non-electronic) methods.

A previous review conducted by (Wofford 2008 (101)) examined the best strategies for patient education about anticoagulation with warfarin. In this review a total of 32 articles were ultimately used for data extraction. Thirteen articles adequately described features of the educational strategy. Five programs used a nurse or pharmacist, four used a physician, and two studies used other personnel/vehicles (lay educators, videotapes). Although 12 articles offered information about educational content, the wording and lack of details in the description made it too hard to assign categories of education topics accurately and to compare articles with one another. Also, seventeen articles were reported on the measures of patient knowledge. This review was done to guide future efforts regarding patient education strategies on warfarin as the authors’ advice was that the first step in improving anticoagulants’ outcomes is prioritizing the educational content and using validated instruments for measuring the outcomes of patient education. In this review, the authors reported a variety of different strategies for all aspects of the educational process and they were unable to summarize published efforts due to an underreporting of details rather than the extreme variability among programs.

Another systematic review (Clarke-Smith 2017 (127)) assessed the effects on the TTR of educational and behavioural interventions for oral anticoagulation therapy (OAT) in patients with atrial fibrillation (AF). This review included eight RCT trials with a total of 1215 AF patients and these trials involved; education, decision aids, and self-monitoring plus education. The authors of the review indicated that because of insufficient evidence, they could not draw definitive conclusions concerning the impact of educational or behavioural interventions on TTR in AF patients receiving OAT. Hence, more trials are required to examine the impact of interventions on anticoagulation control in AF patients and the mechanisms by which they are successful. This current review reports similar findings to this review about the insufficiency of evidence and the need for more trials to evaluate the effectiveness of the educational interventions.
2. Systematic review

Also, several low-quality studies have explored the design and use of electronic programs to improve warfarin knowledge among patients. In addition, two good-quality studies were; the study of [Guo 2017 (134)], appears to be the first prospective randomized trial using mobile health technology for patients with atrial fibrillation. We did not include it in our review because the study target population were patients with AF and the patient knowledge was a focus on atrial fibrillation management rather than on warfarin medication knowledge. These researchers designed an app named the mAF app which had the role of combining clinical decision support, education, and patient-involvement strategies, with a view to improving patients’ knowledge, their adherence to drugs, satisfaction, and quality of life. This study found that more than 90% of patients agreed that the mAF app was easy, user-friendly, and useful, and gave a good feedback to their doctors on the mAF app. More importantly, this app showed significantly improvements in patients’ knowledge with the mAF app over time (all \( P < 0.05 \)), while the patients with usual care showed no knowledge improvement. However, a limitation of this study was that the impact on clinical outcomes (stroke, death, bleeds) of the mAF App needs to be obtained in a long-term prospective study with clinical outcome data, which was not the principal objective of the study.

Another cluster randomized, controlled trial [Vormfelde 2014 (135)] on phenprocoumon (vitamin K antagonist), oral anticoagulants and the educational program comprised sessions conducted by practice nurses and consisted of a video presentation followed by a discussion, brochure and a corresponding questionnaire. The patient’s knowledge about oral anticoagulation, was the primary outcome and measured at baseline and after six months of the trial, while the main secondary outcome was time spent in the INR target range. The patients had at least three INR measurements during a period of continuous phenprocoumon use for at least three months, both in the six months before inclusion in the study and in the six months afterward. Other secondary outcomes were complications that had occurred during the trial periods, self-assessed knowledge, and the patient’s opinion about the need for patient education. This study also found practical improvements in knowledge relating to patient safety, but there were no significant effects on the secondary endpoints, i.e., time spent in the INR target range and complications of anticoagulation.

These two randomized, controlled trial studies supported that education using technology had a positive effect on patients’ knowledge, while both of them reported a limitation on the clinical outcomes. This review has a similar finding to these studies.
Three pilot studies were also identified. In that of (Lee 2016 (136)), the education program was the MASS program for elderly patients, the (Denizaed-Thompson 2012 (137)) study evaluated a three-part series of handheld, multimedia computer iPod™-based patient educational modules given to anticoagulated patients at the time of routine INR blood tests for outpatients on the anticoagulation registry at an urban community health center, and research undertaken by (Faddoul 2012 (138)) investigated games about warfarin and vitamin K, assessing the usability of this game in adult patients. This game educates patients about vitamin K content in certain foods and helps them in learning how they can balance vitamin K intake in their daily diet. The game contains a total of 52 food choices with various vitamin K content arranged in four food categories; fruits, vegetables, meats, and condiments, and it displays instructions both in text and through audio-interface items (messages, hints, and buttons). The storyboard of the game described an individual shopping in a supermarket, and the player adds foods to the shopping cart by clicking on the foods, and this game also has many instructions regarding which how the player can win or lose in the game.

The two pilot studies (Denizaed-Thompson 2012, Faddoul 2012 (137, 138)) did not assess patients’ knowledge during the study process and also they did not assess clinical outcomes (i.e. INR, bleeding and thrombosis complications). These studies measured patient acceptability and usability for the educational programs and game and they reported that the patients were satisfied with the game in the Faddoul 2012 study while in the Denizaed-Thompson 2012 study, patients reported their educational experience with the computer modules was helpful compared with their previous warfarin education. The pilot study by (Lee 2016 (136)) assessed oral anticoagulant knowledge using the OAK test (103), anticoagulant treatment expectations, patients’ self-reported adherence by Morisky medication adherence scale (MMAS) (93), QOL, and depressive and anxiety symptoms. This pilot study found a significant increase in anticoagulation knowledge 3-month after the intervention while there was no significant change in self-reported medication adherence and treatment effectiveness. In addition, patients reported satisfaction with MASS program use, while this study did not assess clinical outcomes.

These pilot studies showed the patients' satisfaction with their programs and patient acceptability to use technology for improving their knowledge of warfarin, which may help future studies to focus on these programs for knowledge development and the impact of these programs on clinical outcomes.

One prospective cohort (Bauman 2009 (139)) study was on the KIDCLOT-POC© program on warfarin for children and their caregivers. This study found that the program promotes high
2. Systematic review

knowledge development and retention in children and caregivers, as the knowledge retention (KR) test scores after 18-24 months post intervention were higher than post intervention scores 7 days after the intervention, and this indicated continued knowledge growth over time. Also, the TTR for children within this study was high (81.7%), with no adverse events reported. Such improvement in knowledge over time and in clinical outcomes in this study would appear to merit inclusion here, but because this study was not a RCT, we excluded it.
2.7. AUTHORS' CONCLUSIONS

2.7.1. Implications for practice

While the studies included in the current review suggested positive effects of electronic education on warfarin patients, their small size and heterogeneous nature means the findings are limited in their value, and we were unable to carry a meta-analysis study. Also, we have very little confidence in the findings, and cannot make recommendations for practice. In (Talboom-Kamp 2017 (131)) study, the authors recommended that more studies are required, preferably to be with larger sample groups and including non-users in which to acquire more insight into the preferences of various patient groups including the related costs. However, (Moore 2015 (130)) study recommended that future studies need to evaluate the effect of video counselling in new start warfarin patients and the use of video counselling in other therapeutic areas should be explored. Otherwise, (Clarke-Smith 2013 (129)) did not give any recommendation for future studies.

2.7.2. Implications for research

Although included studies were RCTs, and from them electronic counselling appeared to have positive effects on patient knowledge, the differences in the interventions’ types and methods, knowledge content and knowledge tests make overall conclusions challenging. All these resulted in low-quality evidence.

Furthermore, since small sample sizes lower the power of studies, less reliance can be placed on these trials. As a result, we recommend that more, adequately powered, good quality, randomized studies should be conducted.

For future studies, it would be of particular value if for similar interventions (e.g., educational video on a smartphone, screen in pharmacy or iPad) comparable validated knowledge tests were used, so that similar outcomes can be pooled across studies.
2. Systematic review

2.8. DATA AND ANALYSIS

This review has no meta-analysis because of the heterogeneity of the outcomes and outcome measures in the included studies.

2.9. CHARACTERISTICS OF STUDIES

2.9.1. Characteristics of included studies

Table 2.3: Characteristics of Clarkesmith 2013 study. (129)

<table>
<thead>
<tr>
<th>Methods</th>
<th>Study Design: Randomised controlled trial.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Blindess: Not blinded.</td>
</tr>
<tr>
<td></td>
<td>Duration of participants: 12 months.</td>
</tr>
<tr>
<td>Participants</td>
<td>Sample size: 97 warfarin-naive AF patients.</td>
</tr>
<tr>
<td></td>
<td>Setting: All patients attending a specialist AF clinic or local anticoagulation outpatient clinic, Birmingham, United Kingdom.</td>
</tr>
<tr>
<td></td>
<td>Inclusion criteria:</td>
</tr>
<tr>
<td></td>
<td>- Patients attending a specialist AF clinic or local anticoagulation outpatient clinic, with documented AF.</td>
</tr>
<tr>
<td></td>
<td>- They were warfarin-naive (having never taken warfarin).</td>
</tr>
<tr>
<td></td>
<td>- They were accepting of OAC therapy.</td>
</tr>
<tr>
<td></td>
<td>- They were approached to participate in the TREAT study.</td>
</tr>
<tr>
<td></td>
<td>Exclusion criteria:</td>
</tr>
<tr>
<td></td>
<td>- Patients were aged &lt;18 years old.</td>
</tr>
<tr>
<td></td>
<td>- They had any contraindication to warfarin.</td>
</tr>
<tr>
<td></td>
<td>- They had previously received warfarin.</td>
</tr>
<tr>
<td></td>
<td>- They had valvular heart disease.</td>
</tr>
</tbody>
</table>
- They were cognitively impaired or had dementia.
- They were unable to speak or read English.
- They had any disease likely to cause their death within the subsequent 12 months.

<table>
<thead>
<tr>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>- A telephone or face-to-face interview permitted the collection of socio-demographic data including: age, gender, occupational status, number of years in education, postcode and ethnicity.</td>
</tr>
<tr>
<td>- Hospital records allowed for collection of baseline clinical measures (e.g. body mass index (BMI), AF history, ECG, blood pressure, left ventricular function, medication) and verification of socio-demographic information.</td>
</tr>
<tr>
<td>- Patients completed a series of postal questionnaires on five occasions: baseline, 1, 2, 6 and 12 months.</td>
</tr>
</tbody>
</table>

**These questionnaires were:**

- The Beliefs about Medication Scale, an 18-item questionnaire.
- The Hospital Anxiety and Depression Scale.
- The Common Sense Model, assessing patients perceptions surrounding their illness (AF).
- Atrial Fibrillation Quality of Life (QoL) Questionnaire, an 18-item health-related QoL scale.
- The Patient Knowledge Questionnaire (14 items).

**Intervention group:** N=46 participants.

- Patients attended one group session [between 1–6 patients] for one hour.
- They were shown a DVD of information about the need for OAC, the risks and benefits associated with OAC therapy, potential interactions with food, drugs, and alcohol, and the importance of monitoring, and control of their INR.
2. Systematic review

Patients were encouraged to ask questions and complete a worksheet-based exercise following each 10 minute DVD section.

**Control group:** N=51 participants.

Patients received the standard ‘**yellow booklet**’ to identify that they are taking OAC therapy.

**The booklet contains:**

- generic information for all patients taking OAC (including deep vein thrombosis, pulmonary embolism etc).
- key safety information including dietary advice (a brief paragraph instructing patients not to miss meals and keep their diet stable).
- medication (to inform GP/physician if they start a new medication).
- emergency contact information.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>The primary outcome:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Time within therapeutic range (TTR).</td>
</tr>
</tbody>
</table>

**The secondary outcomes:**

- Patient’ knowledge.
- Quality of life.
- Anxiety/depression.
- Beliefs about medication.
- Illness perceptions.
- Adverse events (death, thromboembolic, stroke major bleeding, and myocardial infarction).

| Notes | - |
### Methods

- **Study design:** Prospective, randomized open, parallel-group study.
- **Blinded:** Not blinded.
- **Duration of participants:** Seven days.

### Participants

- **Sample Size:** 40 individuals, 17 new start (warfarin naive) patients and 23 restart (Prior warfarin use) patients.
- **Setting:** University of North Carolina Medical Center (UNCMC).
- **Inclusion criteria:**
  - Language: English speakers
  - Age: Adults (≥ 18 years of age)
  - Patient types: warfarin users.
- **Exclusion criteria:**
  - Patients had:
    - cognitive impairment or dementia.
    - under contact precautions.
    - pregnant women.
    - previously exposed to the videos.
    - non-English speaker.

### Interventions

- **Intervention group:**
  - N= 9 new start (warfarin naive) and 11 restart (Prior warfarin use).
  - The participants received informational video recording on tablet device.
2. Systematic review

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Primary outcome:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- The difference in pharmacist time spent counselling (“total time”) between the video and face-to-face counselling groups.</td>
</tr>
<tr>
<td></td>
<td>- Total time included time for scripted counselling, “teach-back” questions, and follow-up questions from study participants, including questions unrelated to anticoagulation therapy.</td>
</tr>
<tr>
<td></td>
<td>Secondary outcome:</td>
</tr>
<tr>
<td></td>
<td>- Participant comprehension as measured by OAK test.</td>
</tr>
</tbody>
</table>

Notes

Control group:

N= 8 new start (warfarin naive) and 12 restart (Prior warfarin use).

The participants received face-to-face oral counselling by 1 of 3 pharmacy counsellors using standardized script with identical information of the video.

"Teach-back" questions used in both groups.
Table 2.5: Characteristics of Talboom-Kamp 2017 study. (131)

<table>
<thead>
<tr>
<th>Methods</th>
<th>Study Design: Parallel cohort design with two randomized self-management groups and usual care group.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Blinded: <strong>Not blinded.</strong></td>
</tr>
<tr>
<td></td>
<td>Duration of participants: <strong>18 months.</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participants</th>
<th>Sample size: 247 participants.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Setting: Primary Care Thrombosis Service Center, Netherland.</td>
</tr>
<tr>
<td></td>
<td>Inclusion criteria: Patients willing to start with self-management, with a long-term indication for anticoagulants, internet access and stable INR values.</td>
</tr>
<tr>
<td></td>
<td>Exclusion criteria: Not stated.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Two randomised self-management groups (e-learning and group training) and a group receiving usual care.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Intervention group:</strong> N=137 participants.</td>
</tr>
<tr>
<td></td>
<td>-Patients were randomly divided into group 1 and 2 using a computer program.</td>
</tr>
<tr>
<td></td>
<td>-After randomisation, 63 patients were included in group 1 (e-learning) and 74 in group 2 (group training).</td>
</tr>
<tr>
<td></td>
<td>-<strong>Group 1:</strong> training was provided by online self-management portal is called Portavita.</td>
</tr>
<tr>
<td></td>
<td>-<strong>Group 2:</strong> face-to-face training was carried out by specialised and expert healthcare professionals.</td>
</tr>
</tbody>
</table>
Both training methods had the same content but were offered in a completely different manner.

**Online self-management portal (Portavita)**

- 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.

- 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.

- 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.

**Control group:** N=110 participants.

- Patients continued to receive regular care (group 3).

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>The primary outcome:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Therapeutic control expressed as the INR control over time (Time in therapeutic range (TTR)) and severe complications (bleedings and thromboembolic events).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>The secondary outcomes:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Usage of an eHealth platform:</td>
</tr>
</tbody>
</table>

Self-management skills were defined as usage of the self-management platform, reflected as the amount of login sessions.
<table>
<thead>
<tr>
<th>Notes</th>
<th>-</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Self-monitoring and self-dosage are registered within the same login session. The usage counts were analysed.</strong></td>
<td></td>
</tr>
<tr>
<td>-Self-Efficacy was measured by Generalised Self-Efficacy Scale(GSES).</td>
<td></td>
</tr>
<tr>
<td>-Quality of life (QoL), which was assessed using the EuroQol-5D (EQ-5D) and displayed at baseline.</td>
<td></td>
</tr>
<tr>
<td>“The EQ-5D is a five-item questionnaire with a higher score reflecting a higher QoL”.</td>
<td></td>
</tr>
</tbody>
</table>
2. Systematic review

2.9.2. Risk of bias for the included studies tables

*Table 2.6: Risk of bias for Clarkesmith 2013 study.* (129)

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>“A computer generated list stratified by age (&lt;70 and ≥70 years)/sex and specialist AF clinic versus ‘general’ cardiology clinic, in blocks of four, randomised patients on an individual basis to receive either ‘usual care’ or the intensive educational intervention” <em>(Randomisation and masking section).</em></td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>“The random allocation was obtained by the researcher telephoning an associate researcher (not involved in the data collection or data entry). A third researcher (not involved in the data analysis or intervention delivery) matched patient identification numbers with randomisation codes and checked the completeness of follow-up questionnaires, and contacted patients via telephone if any questions were not completed” <em>(Randomisation and masking section).</em></td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Unclear risk</td>
<td>Due to the nature of the intervention, patients were not blind to receiving the video, but it's not clear if the patients knew they</td>
</tr>
</tbody>
</table>
2. Systematic review

<table>
<thead>
<tr>
<th>Domain</th>
<th>Risk</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>&quot;A third researcher (not involved in the data analysis or intervention delivery) matched patient identification numbers with randomisation codes and checked the completeness of follow-up questionnaires, and contacted patients via telephone if any questions were not completed&quot; <em>(Randomisation and masking section).</em></td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>High risk</td>
<td>The intervention group=46 and only 43 received the intervention as three of patients switched to the usual care group, the number of patients to dropout from the group during the follow up was five patients. On other hand, the usual care group=51 and after the extra three patients were added the number of patients that received usual care was 54, while the number of patients to dropout from the group during the follow up was one patient.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>The protocol is available separately and they reported the positive and the negative results except for the cost-effectiveness analysis, we contacted the author by email to ask him about the results and no response was received.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>No further concerns.</td>
</tr>
</tbody>
</table>

were on the intervention group or not.
2. Systematic review

*Table 2.7: Risk of bias for Moore 2015 study.*

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Study participants were randomly allocated by block randomization scheme (blocks of 8, 6, 4, or 2) <em>(study protocol section).</em></td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>&quot;A co-investigator who was not involved in the conduct of the study (JHH) generated the randomization schedule.....&quot;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&quot;No investigators involved in the conduct of the study had access to the schedule until study interventions, measurements, and analyses were completed.&quot; <em>(study protocol section).</em></td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>High risk</td>
<td>&quot;The study intervention could not be blinded and the design required staggered participant enrolment, was used to maintain counsellor blinding until the participant was formally enrolled&quot; <em>(study protocol section).</em></td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>&quot;No investigators involved in the conduct of the study had access to the schedule until study interventions, measurements, and analyses were completed&quot; <em>(study protocol section).</em></td>
</tr>
<tr>
<td>Bias Type</td>
<td>Risk Level</td>
<td>Notes</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>High risk</td>
<td>For Restart participants &quot;one participant in the video group was not included in the primary end point analysis because of missing socioeconomic status; however, use of an imputed value to include this participant did not change study results&quot;.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&quot;There was a similar distribution across socioeconomic categories. As noted previously, OAK test scores were missing for 2 participants at baseline&quot; (result section).</td>
</tr>
<tr>
<td>Selective reporting</td>
<td>High risk</td>
<td>The protocol is not available separately and inserted it as part of the method.</td>
</tr>
<tr>
<td>Other bias</td>
<td>High risk</td>
<td>&quot;Unfortunately, a non-significant reduction was observed in New Start participants, although it is unclear if this finding was a result of the small sample size or other factors, such as the increased time required for teach-back questions. The additional time required for teach-back questions may reflect a need to reinforce new information. As such, additional studies are needed to establish if counselling time can be reduced in warfarin-naive participants&quot; (discussion section).</td>
</tr>
</tbody>
</table>
2. Systematic review

Table 2.8: Risk of bias for Talboom-Kamp 2017 study.(131)

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>High risk</td>
<td>&quot;A random selection of 1632 patients was approached for participation in the present study using three methods, (1) information and invitation by letter, (2) personal invitation by specialized nurses and (3) invitation by telephone&quot;. Patients who did not wish to start with self-management were invited to participate in a parallel cohort group receiving usual care (group 3)&quot; (recruitment of patients and non-participation section).</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>High risk</td>
<td>&quot;Patients were free to volunteer, bias might have occurred in our study groups&quot; (the strengths and limitations section). Participants had the ability to choose which group to recruit in, so no allocation concealment was possible.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>High risk</td>
<td>As a result of the Participants having the ability to choose which group to participate in, the blinding of participants and personnel (performance bias) was deemed high risk.</td>
</tr>
<tr>
<td>Bias Type</td>
<td>Level</td>
<td>Description</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>--------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>High</td>
<td>The participants were not blinded, so the subjective outcome results may have been influenced.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>High</td>
<td>&quot;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. 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&quot; (the strengths and limitations section).</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low</td>
<td>The protocol is available separately and all pre-specified outcomes of interest to the review reported in the pre-specified way, except the cost-effectiveness analysis, we contacted the author by email to ask him about the results and his answer was that he is still working on it.</td>
</tr>
</tbody>
</table>
2. Systematic review

<table>
<thead>
<tr>
<th>Other bias</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&quot;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, that is, patients cannot be denied or forced to start with self-management&quot; (the strengths and limitations section).</td>
</tr>
</tbody>
</table>


2.9.3. Characteristics of excluded studies

*Table 2.9: The 25 excluded full-text articles, with reasons.*

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assawasuwannakit 2016 (140)</td>
<td>Not related to warfarin.</td>
</tr>
<tr>
<td>Bauman 2009 (139)</td>
<td>No control arm (pre-post intervention).</td>
</tr>
<tr>
<td>Chenot 2014 (125)</td>
<td>A baseline survey.</td>
</tr>
<tr>
<td>Chrischilles 2014 (141)</td>
<td>No specific result for warfarin patients.</td>
</tr>
<tr>
<td>Denizard-Thompson 2012 (137)</td>
<td>Pilot study.</td>
</tr>
<tr>
<td>Desteghe 2017 (142)</td>
<td>Not related to warfarin, it’s on DOACs, pilot study.</td>
</tr>
<tr>
<td>Faddoul 2012 (138)</td>
<td>No control arm, pilot study.</td>
</tr>
<tr>
<td>Hall 2010 (143)</td>
<td>Systematic review.</td>
</tr>
<tr>
<td>Hendriks 2015 (144)</td>
<td>Not related to educational intervention.</td>
</tr>
<tr>
<td>Holbrook 2007 (146)</td>
<td>No control arm</td>
</tr>
<tr>
<td>Kim 2015 (147)</td>
<td>No control arm, pre-post video knowledge test.</td>
</tr>
<tr>
<td>Lee 2016 (136)</td>
<td>Had single arm (no control arm), pilot study, pre-post design.</td>
</tr>
<tr>
<td>Newall 2008 (148)</td>
<td>No control arm, pilot study.</td>
</tr>
<tr>
<td>Nieuwlaat 2016 (149)</td>
<td>Invited Commentary for meta-analysis with title (Mobile Telephone Text</td>
</tr>
</tbody>
</table>
2. Systematic review

<table>
<thead>
<tr>
<th>Reference</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prochaska 2017 (150)</td>
<td>Not RCT, it's a two-armed, prospective, multicenter cohort study.</td>
</tr>
<tr>
<td>Shuaib 2014 (152)</td>
<td>Online survey on 200 patients, No education intervention.</td>
</tr>
<tr>
<td>Smith 2011 (154)</td>
<td>Letter to the editor.</td>
</tr>
<tr>
<td>Vormfelde 2014 (135)</td>
<td>Not related to warfarin, it's on phenprocoumon (VKA).</td>
</tr>
<tr>
<td>Víquez-Jaikel 2017 (155)</td>
<td>Not related to electronic education, (four phases done by clinical pharmacists) .</td>
</tr>
<tr>
<td>Winans 2010 (110)</td>
<td>Not related to electronic education.</td>
</tr>
<tr>
<td>Witt 2005 (156)</td>
<td>Not RCT, It's observational cohort study.</td>
</tr>
<tr>
<td>Wofford 2008 (157)</td>
<td>Systematic review.</td>
</tr>
<tr>
<td>Xu 2015 (158)</td>
<td>Letter to the editor.</td>
</tr>
</tbody>
</table>
### 2.9.4. Characteristics of ongoing studies

Table 2.10: Characteristics of ongoing study table

<table>
<thead>
<tr>
<th>NCT03125668 (128)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Authors’ names</strong></td>
<td>Rafaela O Manzato.</td>
</tr>
<tr>
<td></td>
<td>Rosana S Dantas.</td>
</tr>
<tr>
<td><strong>Study name</strong></td>
<td>Impact of telephone follow-up in patient's health-related quality of life that use warfarin.</td>
</tr>
<tr>
<td><strong>Methods</strong></td>
<td>Randomized controlled trial (RCT).</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td><strong>Setting:</strong> Hospital das Clínicas, Medical School of Ribeirão Preto, University of São Paulo, Brazil.</td>
</tr>
<tr>
<td></td>
<td><strong>Inclusion Criteria:</strong></td>
</tr>
<tr>
<td></td>
<td>- Age over 18 years.</td>
</tr>
<tr>
<td></td>
<td>- Both genders.</td>
</tr>
<tr>
<td></td>
<td>- They start the use of Warfarin for the first time during the current hospitalization.</td>
</tr>
<tr>
<td></td>
<td>- They have a phone.</td>
</tr>
<tr>
<td></td>
<td><strong>Exclusion Criteria:</strong></td>
</tr>
<tr>
<td></td>
<td>- They start oral Anticoagulation Therapy with another oral anticoagulant.</td>
</tr>
<tr>
<td></td>
<td>- They start warfarin for surgical procedures.</td>
</tr>
<tr>
<td></td>
<td>- They have visual or hearing impairments.</td>
</tr>
<tr>
<td></td>
<td>- They Don’t have cognitive conditions.</td>
</tr>
<tr>
<td></td>
<td>- They have a cancer diagnosis.</td>
</tr>
</tbody>
</table>
| Interventions | Intervention group:  
At the hospitalization, patients receive the educational program (Power Point® Slides, booklets and orientation) about the use of warfarin. After hospital discharge they receive a telephone follow-up (five calls) and two Face to face counselling.  
Control group:  
At the hospitalization, patients receive the educational program (Power Point® Slides, booklets and orientation) about the use of warfarin. After hospital discharge they receive two face to face counselling. |
|---|---|
| Outcomes | Primary outcome:  
- Change in health-related Quality of Life (Time frame: Three and six months after hospital discharge).  
Secondary outcomes:  
- Change in symptoms of anxiety and depression (Time frame: At baseline, Three and six months after hospital discharge).  
- Adherence (Time frame: INR values during the six months follow-up).  
- Assessment and frequency of adverse events related to warfarin (Time frame: Three and six months after hospital discharge). |
| Starting date | 1/October/2015. |
| Contact information | Rafaela O Manzato, PhD Student, contact number: +5517996025036, email: rafamanzato@hotmail.com. |
2. Systematic review

Figure 2.2: Risk of bias graph: review authors’ judgements about each risk of bias item presented as percentages across all included studies.

Figure 2.3: Risk of bias summary: review authors’ judgements about each risk of bias item for each included study.
2. Systematic review
3. **Warfarin Electronic Education Program Pilot Study**

3.1. **BACKGROUND**

The inappropriate use of warfarin results in an increased risk of adverse effects and serious complications. Several studies have found that patients had a low level of warfarin knowledge. (109, 117, 159) This gap can be filled by providing appropriate education on warfarin and developing educational strategies and resources for the purpose of improving patients’ knowledge. (109, 117) Community pharmacists can play an important role in improving their patients’ knowledge of their medication and hence reducing the likelihood of drug interactions and adverse effects. (160)

According to the Pharmaceutical Society of Ireland (PSI), in Ireland the pharmacist ratio per community pharmacy is low at 2.9 per pharmacy. (161) According to a community pharmacy baseline survey study conducted in 2011, most pharmacists spend their working time on dispensing medicines and counselling patients on their prescription and non-prescription medicines. (162) Also, the survey indicated that pharmacists would like to increase the ratio of pharmacists per pharmacy to help them improve the quality of pharmacy services, such as increasing the counselling time for patients and building new services, (162) but this is not practical because employing additional qualified pharmacists is costly. Moreover, not every patient collects their prescription themselves, so even if there were more pharmacists in the pharmacy they might not be able to counsel all patients effectively. Hence, our target is to use technology to improve counselling services and hopefully lead to improvements in patients' knowledge of their treatment (in this case warfarin treatment). The objective of this pilot study was to develop and trial an electronic tool to assess participants’ knowledge regarding their warfarin therapy and to provide education on key aspects of their medication.
3. Warfarin pilot study

3.2. AIMS AND OBJECTIVES

3.2.1. Study aims

The aims of this study were to:

- Create and evaluate a new electronic educational program for warfarin patients.
- Appraise the effectiveness of the digital intervention for improving patients’ knowledge of their warfarin treatment.

3.2.2. Objectives

Specifically, the objectives of this study were to:

- Design a new warfarin education program using technology that gives flexibility to the patient to learn about his/her medication.
- Pilot the new program on warfarin patients to determine the feasibility and acceptability of using it in the pharmacy clinical environment.
- Examine the impact of the education program on patients’ warfarin knowledge.
3.3. METHODS

3.3.1. Study design and setting
A pilot study was performed in the community pharmacy setting (nationwide, Ireland) between 19th February and 2nd March 2018 by second-year pharmacy undergraduates (Senior Freshman, School of Pharmacy and Pharmaceutical Sciences, Trinity College Dublin). The study was approved by the School of Pharmacy and Pharmaceutical Sciences Research Ethics Committee.

3.3.2. Participants in the study
All adult patients receiving warfarin attending the pharmacies where the students were placed, who were over 18 years old, could speak and read English, and who could use a suitable electronic device (e.g. smartphone, iPad, tablet, or laptop) were eligible for inclusion in the study. Patients who were blind, had cognitive impairment or dementia, and those who were pregnant, were excluded from the study. A convenience sample of patients was recruited and informed consent was obtained from the patients before they received the electronic program of warfarin counselling, delivered using their or the students’ personal mobile devices. The students explained the program to the patients and helped them in using it for the first time, although the program is designed for use multiple times subsequently. The patients undertook a preliminary knowledge test before they received the warfarin educational program, and directly after they finished the program they undertook a second knowledge test.

3.3.3. Study outcomes
Improvement in the patients’ knowledge regarding their warfarin therapy. This was measured by using a validated anticoagulation knowledge assessment (AKA) test previously developed by Briggs et al. (102)

3.3.4. Intervention development
Articulate 360, version 1.11.14180.0 (Articulate Global, Inc., New York, USA) was used to design our education program. The reason for choosing this software was that it had the tools to facilitate the design of an interactive program without the requirement for advanced computer coding skills.

Furthermore, it was possible using this software to generate an educational program with the same display, navigation and performance irrespective of the device platform used by the participants, owing to the embedded Articulate Player.
3. Warfarin pilot study

The education program consisted of three main sections: a pre-education test of knowledge, an education section, and a post-education knowledge test. The education section was divided into four parts, each part containing several topics. The topics covered in the first part were about how warfarin is used, brands and strengths, side effects, pregnancy and breast feeding, and action to be taken in case of a missed dose. In the second part, the topics concerned INR measurement. The third part covered the interactions of warfarin. Finally, the fourth part covered the contraindications, action in case of a surgical or dental appointment, signs of overdose and under-dose, precautions, and advice in case of travel.

The AKA Questionnaire was used for the pre-education knowledge test and post-education knowledge test. The AKA questionnaire is a validated 29-item questionnaire (see appendix 2) (102), with closed-ended questions (multiple choice answer-style questions). This questionnaire addressed most of the topics in the education program and the multiple choice answers were time-saving for the patients and allowed an objective score to be calculated. Also, since this questionnaire has been widely used for assessing the OAT knowledge of participants, it facilitates comparison with other studies. Minor modifications were made to the original AKA test to make it compatible with the Irish market (i.e. adjustment of medicine brand names and food brands.) The pre-education test was a standard multiple choice questionnaire with text alone, but the post-knowledge test was presented as a game with interactive questions that allowed the patient, for example, to drop something in a bag, choose a picture explaining the situation, or drag something to one place (see Figure 3.1). The intended benefit from this way of education was to encourage the patients to learn about their health information in an easy, convenient but engaging way and hence reach a better outcome. (138, 163, 164) Studies that develop interactive games use visual, textual, and auditory channels, and they give immediate feedback that promotes the patients’ learning. (138, 164)

The knowledge tests were integrated with the warfarin education program so the patient could progress from one component to the next without the need for technical expertise: the first test, then the education program, and finally the second test. Patients who answered at least 21 questions correctly were deemed to have attained a passing score (i.e. an adequate level of warfarin knowledge) in accordance with Ryals et al. study, equivalent to 72.4% (each question representing 3.45 percentage points and with zero points for incorrectly answered questions. (100)
3. Warfarin pilot study

Figure 3.1: Display for different sections of pre- and post-knowledge test items of the electronic program
3. Warfarin pilot study

3.3.5. Intervention administration

Owing to individual patients’ needs, pharmacists’ intervention at the point of intervention administration was not standardized, other than ensuring that patients completed the questionnaires without prompting and additional counselling was not provided by the pharmacy staff between the baseline and post-education questionnaires (i.e. the education programme including both questionnaires was delivered as an uninterrupted unit so differences pre- and post-education could be attributed to the electronic education rather than pharmacist counselling), although the pharmacist was free to provide additional counselling where necessary outside this unit.

3.3.6. Statistical analysis

The quantitative data collected via the Articulate 360 software was analysed using the IBM Statistical Package for the Social Sciences (SPSS) version 25.0 (IBM Analytics, New York, USA) and Microsoft Excel software, version 16.14.03 (Microsoft Corporation, Washington, USA). In SPSS, descriptive statistics were calculated for the 29 questions and used to compare the percentage of correct answers in tests before and after undertaking the education programme, to find the questions most frequently answered correctly and incorrectly, questions in which there was the most improvement, the least improvement, and the questions that were still answered poorly (< 50% of respondents) after the education program.

The passing score of 72.4% (21/29 questions) was used to determine how many patients passed and how many failed in both the pre-education and post-education knowledge tests. Median scores in the knowledge tests before and after the education program were compared using a paired samples Sign test. Also, the Chi-squared test was used to compare the percentage of patients who passed and failed before/after the education program. A P-value of less than 0.05 was considered to indicate a statistically significant difference.

3.3.7. User feedback

An anonymous online questionnaire was administered to all the second year undergraduate pharmacy students evaluating all aspects of their experiential learning while on placement. Where comments were made by the students relating to the anticoagulant tool and its use, these were extracted by the staff overseeing the student feedback and provided to the researchers. Owing to the small number of responses involved, these comments were reviewed manually without specialist software, to identify common themes.
3.4. RESULTS

A total of 56 participants agreed to participate in the study, and all the patients completed the 29-item questionnaire in full with no missing answers.

3.4.1. Warfarin knowledge test results

The number of patients who passed the test before the education program was 35 (62.5%) patients and 21 (37.5%) failed the test (i.e. they answered fewer than 21 questions correctly, or more than 8 incorrectly). In contrast, 51 (91.1%) passed the knowledge test after the education program and only 5 (8.9%) patients failed. None of the patients achieved a test score of 100% in either test. (See Figure 3.2)

![Figure 3.2: The number of warfarin patients who passed/failed in both pre- and post-education tests: baseline statistics](image-url)
3. Warfarin pilot study

The question which was most frequently answered correctly was question number 17: ‘While taking warfarin, which of the following represents a situation when you should go to the emergency room?’ (in case of emergency) with 100% (56/56) of patients answering correctly both before and after the education program. In contrast, the question which was least frequently answered correctly was question number 4: ‘You just remembered that you forgot to take your evening warfarin medication dose last night. You would…-‘ (in case of missing dose) with only 28.6% (16/56) patients answering correctly before the program, and 71.4% (40/56) answered incorrectly, while 42.9% (24/56) answering correctly after the program and 57.1% (32/56) answered incorrectly. (See Table 3.1)

The question showing the most improvement in knowledge after education was number 9: ‘which of the following is an effect of warfarin medication that will most likely be experienced?’ (adverse effect) with 60.7% (34/56) patients answering correctly in the second test compared with 28.6% (16/56) prior to education. (See Table 3.1)

Little improvement was seen for questions 4 (action in case of a missed dose) which was the least frequently answered correct question, question 5 (food-drug interaction) with 48.2% (27/56) patients answering correctly “can eat spinach but need to eat the same amount regularly every week” in the second test compared with 21.4% (12/56) prior to education, as 58.9% (33/56) of the patients answered incorrectly “should not eat spinach” before the education compared with 46.4% (26/56) in the second test. (See Table 3.1)

The questions showing no improvement in knowledge after the education program were questions number 8 (compliance with the dose and recommendations – action if the patient ran out of medicine) and number 14 (compliance with the dose and recommendations – the best time of day to take warfarin) with 98.2% (55/56) after the education program and 98.2% (55/56) prior to education. (See Table 3.1)

Three questions continued to be answered poorly (less than 50% of the patients answered correctly) after the education program, namely questions 4 (action in case of a missed dose the previous day), 5 (whether the patient could eat spinach), and 16 (interactions with beverages). Question number 4; 57.1% (32/56) of the patients answered incorrectly with “take the missed dose right now” while the correct answer was “skip the dose of warfarin you missed”, Question number 5; 48.2% (27/56) of patients answered incorrectly with “should not eat spinach” while the correct answer was “can eat spinach but need to eat the same amount regularly every week”, and question number 16; 50% (28/56) of the patients answered incorrectly with
3. Warfarin pilot study

“Tropicana orange juice” and the correct answer was “Ensure nutritional supplement shake”.

See Table 3.1.
Table 3.1: Test results for each question before and after the education program

<table>
<thead>
<tr>
<th>Questions No.</th>
<th>Question topic</th>
<th>Number (%) of correct answers before the education program (n=56)</th>
<th>Number (%) of correct answers after the education program (n=56)</th>
<th>The most/least frequently answered correctly</th>
<th>The most/least improvement in knowledge after education</th>
<th>No improvement</th>
<th>Answered correctly by &lt; 50% of participants after education</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
<td>Suitable analgesics</td>
<td>48 (85.7%)</td>
<td>52 (92.9%)</td>
<td></td>
<td></td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Q2</td>
<td>Food-drug interactions 1</td>
<td>33 (58.9%)</td>
<td>49 (87.5%)</td>
<td></td>
<td></td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Q3</td>
<td>Urgent treatment required 1</td>
<td>50 (89.3%)</td>
<td>54 (96.4%)</td>
<td></td>
<td></td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Q4</td>
<td>Missing dose</td>
<td>16 (28.6%)</td>
<td>24 (42.9%)</td>
<td>The least frequently answered correctly</td>
<td>The least improvement in knowledge after education</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Q5</td>
<td>Food-drug interactions 2</td>
<td>12 (21.4%)</td>
<td>27 (48.2%)</td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Q6</td>
<td>Alcohol-drug interactions</td>
<td>18 (32.1%)</td>
<td>33 (58.9%)</td>
<td></td>
<td></td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Q7</td>
<td>OTC multivitamin use</td>
<td>38 (67.9%)</td>
<td>47 (83.9%)</td>
<td></td>
<td></td>
<td></td>
<td>No</td>
</tr>
</tbody>
</table>
### 3. Warfarin Pilot Study

<table>
<thead>
<tr>
<th>Questions No.</th>
<th>Question topic</th>
<th>Number (%) of correct answers before the education program (n=56)</th>
<th>Number (%) of correct answers after the education program (n=56)</th>
<th>The most/least frequently answered correctly</th>
<th>The most/least improvement in knowledge after education</th>
<th>No improvement</th>
<th>Answered correctly by &lt; 50% of participants after education</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q8</td>
<td>Running out of medicine</td>
<td>55 (98.2%)</td>
<td>55 (98.2%)</td>
<td></td>
<td>No improvement</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Q9</td>
<td>Common side effects</td>
<td>16 (28.6%)</td>
<td>34 (60.7%)</td>
<td>The most improvement in knowledge after education</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Q10</td>
<td>Treating a cold</td>
<td>47 (83.9%)</td>
<td>54 (96.4%)</td>
<td></td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Q11</td>
<td>Informing the dentist</td>
<td>54 (96.4%)</td>
<td>55 (98.2%)</td>
<td></td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Q12</td>
<td>Antibiotics treatment</td>
<td>52 (92.9%)</td>
<td>54 (96.4%)</td>
<td></td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Q13</td>
<td></td>
<td>24 (42.9%)</td>
<td>29 (51.8%)</td>
<td></td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Q14</td>
<td>Dosage time</td>
<td>55 (98.2%)</td>
<td>55 (98.2%)</td>
<td></td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Q15</td>
<td>Sign of high INR</td>
<td>38 (67.9%)</td>
<td>45 (80.4%)</td>
<td></td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Q16</td>
<td>Interaction with drinks</td>
<td>19 (33.9%)</td>
<td>26 (46.4%)</td>
<td></td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q17</td>
<td>Urgent treatment required 2</td>
<td>56 (100%)</td>
<td>56 (100%)</td>
<td>The most frequently</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>
### 3. Warfarin Pilot Study

<table>
<thead>
<tr>
<th>Questions No.</th>
<th>Question topic</th>
<th>Number (%) of correct answers before the education program (n=56)</th>
<th>Number (%) of correct answers after the education program (n=56)</th>
<th>The most/least frequently answered correctly</th>
<th>The most/least improvement in knowledge after education</th>
<th>No improvement</th>
<th>Answered correctly by &lt; 50% of participants after education</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q18</td>
<td>Herbal supplement interactions</td>
<td>54 (96.4%)</td>
<td>55 (98.2%)</td>
<td>answered correctly</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q19</td>
<td>Monitoring 1</td>
<td>41 (73.2%)</td>
<td>44 (78.6%)</td>
<td>No</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q20</td>
<td>Monitoring 2</td>
<td>54 (96.4%)</td>
<td>55 (98.2%)</td>
<td>No</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q21</td>
<td>Less urgent effect</td>
<td>24 (42.9%)</td>
<td>31 (55.4%)</td>
<td>No</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q22</td>
<td>Monitoring 3</td>
<td>49 (87.5%)</td>
<td>54 (96.4%)</td>
<td>No</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q23</td>
<td>Factors influencing efficacy</td>
<td>48 (85.7%)</td>
<td>54 (96.4%)</td>
<td>No</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q24</td>
<td>Urgent treatment required 3</td>
<td>45 (80.4%)</td>
<td>49 (87.5%)</td>
<td>No</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q25</td>
<td>Food-drug interactions 3</td>
<td>33 (58.9%)</td>
<td>41 (73.2%)</td>
<td>No</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q26</td>
<td>Use of generic</td>
<td>48 (85.7%)</td>
<td>51 (91.1%)</td>
<td>No</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q27</td>
<td>The time need for drug to get out of the body</td>
<td>44 (78.6%)</td>
<td>47 (83.9%)</td>
<td>No</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q28</td>
<td>Treatment duration</td>
<td>51 (91.1%)</td>
<td>54 (96.4%)</td>
<td>No</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q29</td>
<td>Risky activities</td>
<td>53 (94.6%)</td>
<td>55 (98.2%)</td>
<td>No</td>
<td>No</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3.4.2. Comparison of warfarin knowledge questionnaire scores before and after education

Warfarin knowledge was found to improve in patients, with a median score of 72.4% (IQR 65.5-79.3) before the education program rising to 86.2% (IQR 79.3-88.8) after the program. A paired samples sign test comparing percentage scores in the knowledge tests before and after education showed a highly significant improvement in scores (Z = -7.001, P < 0.001). Figure 3.3

Figure 3.3: Comparison of the correct scores in the knowledge test before and after education
3. Warfarin pilot study

3.4.3. Influence of prior knowledge

The Chi-squared test was carried out to explore the proportions of patients passing/failing the knowledge test before/after the education program, and it was found to be highly statistically significant with \( P = 0.005 \). This result again indicates that there was a significant improvement in the patients' knowledge after the program. Figure 3.4

![Graph showing the proportion of patients passing/failing the knowledge test before/after the education program.](image)

**Figure 3.4: Proportion of patients passing/failing the knowledge test before/after the education program**

\[** P = 0.005 \] (indicate highly statistical significant)
3.5. DISCUSSION

3.5.1. Warfarin knowledge test

To our knowledge, this pilot study is the first study in Ireland investigating electronic counselling and assessment of patients’ knowledge of their warfarin medication. In the study, 51 of the total 56 patients (91%) passed the knowledge test after the electronic education program. This high percentage is an encouraging result which indicates the tool (with minor modifications in line with feedback – see later) is suitable for a more comprehensive study in a larger sample size.

One Irish study found improvement in the numbers of patients who achieved a passing score from 39.5% to 74.4% after the verbal counselling done by pharmacists. This result indicates the importance of educating patients regarding their warfarin therapy. (106)

The question most frequently answered correctly was the action to take in case of an emergency (question 17). Pourafkari et al. had a similar finding as their patients too answered most correctly for the question about situations that mandate visiting the emergency department, along with the question about the understanding the results of the prothrombin time/INR test. (108)

The topics where the patients demonstrated an inadequate knowledge of warfarin were the action to take in the event of a missing dose the previous day and food-drug interactions. In question number 4, what should they do if they missed a dose, in the education program the information provided was firstly to take the missed dose as soon as you remember, and secondly to skip the dose if it is almost time for your next scheduled dose. It appears that patients may have been confused about the choice between these two situations so they answered according to the first point. Potentially further interactive examples would help.

Question number 5 concerned spinach. In the education program the information about the food-drug interactions was clear “you should keep your vitamin supplement and food intake steady throughout treatment”. However, there was no specific information related to the amount of spinach it might be possible to eat per week, but the point that mentioned in the education program cover all types of food contain vitamin K. Again, a worked example could prove useful.

Education on diet is essential, especially about foods that contain vitamin K. While patients do not need to avoid foods rich in vitamin K, they must be consistent with consumption habits, (10) so we can add for example a small red box in the education program to alert the patients about these information.
3. Warfarin pilot study

Likewise, for question number 16, half of the patients answered incorrectly, which may be due to the patients being unaware of the nutritional content of the drinks mentioned. Potentially use of a more generic phrase (e.g. vitamin/mineral nutritional supplement) rather than the specific Ensure brand would have been preferable to overcome this limitation. It is also possible that the patients’ mistaken belief that orange juice may decrease the effect of their warfarin (similar to the study of Ryals et al. in which 34.1% of the patients chose orange juice instead of the nutritional supplement) may have stemmed from discussion in the clinic regarding other juices, such as cranberry and grapefruit, which can increase the effect of warfarin. (100) Two studies Ryals et al. and Nybo et al. reported that question number 5 (about the spinach) was one of the most incorrectly answered questions in their study, also questions number 4 (missing dose) and 16 (food-drug interaction) for Nybo et al. (81, 100)

From this point, patients need to be educated more effectively in future about the action to take in the event of a missed dose of warfarin, and food-drug interactions with more specific information.

For questions number 8 (compliance with the dose and recommendations – action if the patient ran out of medicine) and number 14 (compliance with the dose and recommendations – the best time of day to take warfarin) there was no improvement as only one patient in each question answered the question incorrectly before and after education.

3.5.2. Pharmacist role in patient education

Pharmacists can play an essential role in improving warfarin patients knowledge by embracing opportunities to deliver professional services to the patients aimed to decrease pharmacists counselling time and transmit the information of the medicine to the patients by using easy to understand and comfortable methods for example; interactive programs with quizzes on their own devices as in our study which allow them to repeat the information many times, educational videos on screen inside the pharmacy, or videos on an iPad. In the Kim et al. study, they found that utilizing a video on iPad was effective, and that most patients reported that they liked using their iPad to educate them about warfarin. (147) Furthermore, the patient can get the benefit from their waiting time in the pharmacy to learn about their medicine and at the same time this allows the pharmacist to know the weak points for each patient and give them short counselling on these points before leaving the pharmacy to ensure that patients have the correct information guiding them to deal with their medicine. Appropriately in the study by Moore et al., it was found that using video technology to educate patients was an efficient method of
education, and significantly reduced pharmacist time required for anticoagulation counselling. (130)

3.5.3. **Comparison of warfarin knowledge questionnaire scores before and after education by using a paired samples sign test instead of a paired samples T-test**

Because the data was not normally distributed we used the median instead of the mean as a measure of central tendency. The result was highly significant after the education and this indicated that the electronic program was practically effective and beneficial.
3. Warfarin pilot study

3.6. USER FEEDBACK

Feedback on the study tools was provided by the pharmacy students who used the tool with their patients, and included comments made to the students by the patients themselves.

Many positive comments on the program were received. For example, some pharmacy students had found it useful to refresh their own knowledge:

- “This was a handy guide. I went through it myself as a reminder.” [Pharmacy student 4]
- “Good refresher.” [Pharmacy student 18]
- “Nice to have the key information in one place.” [Pharmacy student 11]
- “It was helpful for me to be able to go through the main counselling points before going out to a patient.” [Pharmacy student 37]

It also gained the approval of patients:

- “My patient liked it. She said the video made it easier to take in than someone just telling her.” [Pharmacy student 11]
- “It was good for the patients to have something they could go back to in their own time.” [Pharmacy student 28]

However, there were also suggestions for improvement. These could be classified under three interrelated headings: content, format and navigation.

Content

Some of the comments here concerned the questionnaires, with some frustration at the additional burden they imposed.

- “I understand why the questionnaires were needed but they did take quite a lot of time. I think after the study is complete and the questionnaires aren’t needed any more, it will work better.” [Pharmacy student 37]
- “The first quiz didn’t tell you the right answer if you had got it wrong, it just said you had answered incorrectly. This meant that the time spent on that quiz wasn’t really useful to the patient, only the study. Giving the right answer like in the second quiz would have been more helpful.” [Pharmacy student 2]

Overtly testing patients’ knowledge was also considered to be a potential deterrent:

- “Maybe it would be better not to call it a test because this is a bit offputting.” [Pharmacy student 17]
Other comments suggested that some components might not align with certain patients’ experience or were more than they needed:

- “My patient said he mostly deals with his GP now, not the warfarin clinic, but the programme focused on the clinic.” [Pharmacy student 17]
- “Not many patients will be testing themselves. If I were streamlining it, I’d cut down the details on testing equipment etc.” [Pharmacy student 37]

Format

The fact that the information was presented in both visual and audio format was appreciated:

- “Having the audio was a help because my patient could not read the screen easily.” [Pharmacy student 16]
- “Pictures were good – helped make the point.” [Pharmacy student 24]
- “I liked the way the second quiz was more interactive.” [Pharmacy student 21]

However, there was some negative feedback on the use of automatic text-to-speech for the voiceover:

- “Computerised voice was a little annoying.” [Pharmacy student 24]
- “A real voice would have been nicer than the automatic reader.” [Pharmacy student 23]

It was also felt that some of the graphics could be clearer, and large screens were preferable:

- “Some of the pictures could be improved. You could see what they were from the text, but if they were just on their own you wouldn’t necessarily be clear on what they were.” [Pharmacy student 37]
- “For patients with poor eyesight this works better on an iPad than a phone.” [Pharmacy student 27]

Navigation

Comments on navigation mainly centred on the desirability of customizing individual patients’ education experience to focus on the components most relevant to them:

- “The programme is quite long. It would be nice to be able to skip to the bits you’re really interested in.” [Pharmacy student 8]
- “Better if you could leave out parts that aren’t relevant to you, e.g. pregnancy.” [Pharmacy student 20]
3. Warfarin pilot study

3.7. CONCLUSION

The purpose of this pilot study was to assess the effectiveness of utilizing educational technology among warfarin patients and enhance the counselling services in community pharmacies in Ireland.

With respect to using the e-learning software (Articulate 360) to design an interactive educational program, we created an easy, multiple use program, with an interactive knowledge test. For the interactive knowledge test, the AKA test which is a validated 29-item questionnaire, was used to calculate the objective score of the patients.

Pharmacy students at Trinity College Dublin played a vital role in the community pharmacy setting during their training time by teaching patients about the interactive program. So this thesis shows the role of pharmacists in educating the patients and the importance of using the technology for counselling instead of the traditional counselling methods.

The finding of this study shows that the use of an electronic education program to improve the knowledge of warfarin patients had a positive effect and this result encourages us to perform the study on a large cohort of patients.

Concerning the weaker knowledge points according to the patients' results, notably food-drug interactions, and compliance with dose and associated recommendations (in case of running out of medicine or in case of missing dose), we should ameliorate these points by adding some warning notes beside each information in the electronic program.
4. DOAC Electronic Education Program Pilot Study

4.1. BACKGROUND

4.1.1. Warfarin prescribing in Ireland

Warfarin is one of the most commonly prescribed drugs in Ireland. According to the annual reports of the Health Service Executive from 2006 to 2016, warfarin consistently ranks among the drugs that have a high prescribing frequency. For example, looking at the various patient categories in Ireland’s health services, in the general medical services (GMS) warfarin ranked at 14 in 2006 and at 23 in 2016 based on prescribing frequency. (165, 166) Similarly, in the drug payment (DP) scheme, warfarin’s ranking was 26 in 2006 and 34 in 2016, while for the long-term illness (LTI) scheme warfarin ranked at 48 in 2006 and 32 in 2016. (165, 166)

4.1.2. DOAC prescribing in Ireland

Despite the widespread use of warfarin, in Ireland DOAC prescribing is increasing, with a corresponding reduction in prescriptions for warfarin (see Table 4.1), mirroring the international trends mentioned in Chapter 2. A retrospective cohort study of all users of warfarin in the Irish pharmacy claims database from 2012 to 2015 reported that there were 61,627 patients who had received warfarin during the study period and 9382 of those patients (15.2%) switched to at least one of the DOACs during the follow-up period. (167) Recent international studies also found that the proportion of warfarin users has decreased while the use of DOACs is rising rapidly. (47, 168, 169) Factors influencing the increase in DOAC prescribing include the fact that these drugs have the ability to be given in fixed doses, have fewer interactions with food or other drugs, a wide therapeutic window and do not require regular monitoring, compared with warfarin. (51)
Table 4.1: Change in the prescribing frequency (number of prescriptions and frequency ranking) for warfarin and DOACs in Ireland in 2006, 2011, and 2016 according to GMS and DP scheme annual reports. (165, 166, 170)

<table>
<thead>
<tr>
<th></th>
<th>GMS</th>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rank 14</td>
<td></td>
<td>Rank 12</td>
<td>Rank 23</td>
<td>Rank 26</td>
<td>Rank 23</td>
<td>Rank 34</td>
</tr>
<tr>
<td>(540,599)</td>
<td></td>
<td>(737,534)</td>
<td>(504,428)</td>
<td>(93,528)</td>
<td>(85,528)</td>
<td>(43,165)</td>
</tr>
<tr>
<td>DOACs: Apixaban</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>(26,727)</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>-</td>
<td>-</td>
<td>Rank 87</td>
<td>-</td>
<td>-</td>
<td>Rank 42</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(170.108)</td>
<td></td>
<td></td>
<td>(34,843)</td>
</tr>
</tbody>
</table>

4.1.3. Patients’ knowledge of warfarin and the effect of patient education

One survey on patients’ knowledge of warfarin reported that patient awareness was poor about many aspects of taking warfarin and worryingly an area where patients lacked understanding was with regard to the steps to take in case of bleeding. (171) Another area of concern was that 56% of the warfarin patients did not know about any drug interactions, and only 42% knew about some of the adverse effects. (171) Other studies show similar deficiencies in knowledge and understanding. (88, 172) Therefore, the potential benefit from an educational intervention to improve patients' knowledge regarding their oral anticoagulant therapy is clear, with a possible indirect role in improving anticoagulation control, achieving secondary prevention of stroke, and thus, in turn, reducing the load on the health services. (173)

4.1.4. Using technology as a tool to improve patient knowledge

The number of smartphone users in Ireland increased from 2.96 million in 2015 to 3.22 million in 2016, with a forecast up to 4.06 million in 2022. (174) It has also been reported that the majority of internet users in Ireland use their smartphone to use search engines, check email and social media sites at least weekly. (174) Moreover, the use of desktop computers saw a
decline especially among users 55 years of age and older as the usage of the smartphone has seen an increase of 34% in this group since 2012. (174)

In view of this increased access to personal technology, there are new opportunities to use technology to enhance medication knowledge and improve patients’ comprehension about their medication. Previous studies have used electronic counselling by presenting warfarin education on iPads and iPods and they found this way of education effective for many reasons; the small size of the device providing a private educational experience, unlike the other digital devices (i.e. versatile disc player or video cassette recorder), these devices were easily portable, efficient in working via wireless connection, and had no requirement for additional equipment such as a television (137, 147).

Since knowledge and understanding influence behavior, a necessary first step towards improving the outcomes of patients using anticoagulant therapy is prioritizing educational content and using validated instruments for measuring the results of patient education. (101) In this intervention study, the electronic educational program covers key topics about the DOACs, and the AKA is the validated tool to measure the patients’ knowledge.
4.2. AIMS AND OBJECTIVES

4.2.1. Study aims

The aims of this study were to:

- Create and evaluate a new electronic educational program for DOACs patients.
- Assess the effectiveness of the electronic intervention for improving patients’ knowledge regarding their DOACs treatment.

4.2.2. Objectives:

Specifically, the objectives of this study were to:

- Design a new DOACs education program using technology that gives flexibility to the patient to learn about his/her medication.
- Assess the baseline patients’ adherence by developing electronic tools for a Morisky scale questionnaire.
- Pilot the new program on DOACs patients to determine the feasibility and acceptability of using it in the pharmacy clinical environment.
- Appraise the impact of the education program on patients’ DOACs knowledge.
4.3. METHODS

4.3.1. Study design and setting

The pilot study performed in the pharmacist-led outpatient anticoagulation clinics of Tallaght Hospital and the community pharmacies (Dublin, Ireland) between April 2018 and August 2018. The study was approved by the School of Pharmacy and Pharmaceutical Sciences Research Ethics Committee.

4.3.2. Participants in the study

All patients who received DOACs, were over 18 years old, could speak and read English, and who could use electronic devices (smartphone, iPad, tablet, or laptop) were included in the study. We excluded patients who were children (under 18 years), were blind, had cognitive impairment or dementia, those who were pregnant, or patients unable to speak or read English.

Informed consent was obtained for all patients before they were exposed to the electronic program of either warfarin or DOAC counselling according to their prescription.

The patients’ knowledge was measured using a validated anticoagulant knowledge assessment test, consisting of a 20-item questionnaire. The patients undertook the knowledge test before (baseline) and directly after they received their education (post-counselling).

4.3.3. Intervention development

The DOACs electronic education program was developed by using Crazy Talk Animator 3 software, version 3.22.2426.1 Pro (Reallusion Inc, New York, USA) and Articulate 360, version 1.11.14180.0 (Articulate Global, Inc., New York, USA).

The animation for the electronic education program was initially prepared in Crazy Talk Animator 3 software, using the Medical Collection - Professionals Characters, Elastic Motions and Impressive Loops which allow the character to talk and move at the same time. Then, the conversation between the pharmacist and the patient was automatically generated by utilizing the text-to-speech function on the same software. Furthermore, additional components were explicitly drawn for the intervention where necessary. Having prepared small videos for multiple scenes in Crazy Talk Animator 3, these were then collected and embedded in Articulate 360 to look like one video, adding additional components to give the program interactive traits, such as selection of the DOAC in use.
4.DOACs pilot study

As for the warfarin education program, the DOAC education program had the same display, navigation and performance irrespective of the device platform used by the participants, owing to the embedded Articulate Player.

The education program was designed as an interactive video that allowed the patient to feel the environment of the counselling room (i.e., pharmacist and patient conversations about information on the DOACs). Topics covered included the anticoagulants and the purpose of taking them, how to take them, monitoring, side effects and action in case of emergency, drug-drug interactions, food-drug interactions, alcohol-drug interactions, precautions, and action in case of a missed dose.

In order to tailor the information provided to the patients’ specific needs, selection points through the counselling gave the patient the ability to choose what information he/she needed to know; for example, if the patient clicked on which DOAC product he/she was prescribed, they could see the action to be taken in case of missing a dose of that particular drug. (See Figure 4.1).
Figure 4.1: Display for different sections in the interactive video that included in the electronic program
4. DOACs pilot study

The knowledge test was performed before and after the education program as part of the program. The test used in the DOACs electronic program was the validated AKA—a test originally designed for warfarin (102) with minor modifications to it. The final version used as the DOACs knowledge test consisted of 20 items, as nine questions were removed from the original one since the questions were not relevant to DOACs. (See appendix 3.)

In addition to the electronic education program, we developed an electronic version for the Morisky 8-item scale to measure the baseline adherence of the patients.

4.3.4. Intervention administration

Similar to the warfarin education, the needs of individual patients meant that pharmacists’ intervention at the point of intervention administration was not standardized, other than ensuring that patients completed the questionnaires without prompting and additional counselling was not provided by the pharmacy staff between the baseline and post-education questionnaires (i.e. the education programme including both questionnaires was delivered as an uninterrupted unit so differences pre- and post-education could be attributed to the electronic education rather than pharmacist counselling), although the pharmacist was free to provide additional counselling where necessary outside this unit.

4.3.5. Study outcomes

4.3.5.1. Primary outcome

Improvement of patients’ knowledge as demonstrated in the AKA as pre-education test and post-education test. The passing score for the test was 70%. (100, 102)

4.3.5.2. Secondary outcomes

A Morisky 8-item questionnaire was piloted as a part of the education program. (93)

4.3.6. Statistical analysis

The quantitative data collected from the Articulate 360 software was analysed by using the IBM Statistical Package for the Social Sciences (SPSS) statistics version 25.0 (IBM Analytics, New York, USA) and Microsoft Excel software, version 16.14.03 (Microsoft Corporation, Washington, USA). In SPSS, we used the descriptive statistics (frequencies) for the 20 questions to compare the percentage of correct answers in tests before and after undertaking the education programme, to find the questions most frequently answered correctly and incorrectly, questions in which
there was the most improvement, the least improvement, and the questions that were still answered poorly (< 50% of respondents) after the education program.

According to the AKA test for warfarin passing score calculation mentioned in chapter (3) section (3.3.4), we calculated the passing score for DOACs knowledge test as follows:

For 20 questions, the number of correct questions to consider that patient had good level of education was calculated as:

\[
20 \times \frac{21}{29} = 14.48 \approx 14 \text{ correct questions}
\]

The passing percentage: \[
\frac{14}{20} \times 100 = 70\%
\]

For each correct question of the 20 questions had score with: \[
\frac{1 \times 100\%}{20} = 5\%
\]

So, the passing score of the 20-item AKA test for DOACs was 70%, as at least 14 questions should be correct to consider that a patient has the appropriate level of knowledge, with each correct answer scoring 5% and incorrect answers scoring zero. This passing score was used to determine how many patients passed and how many failed in both the pre-education and post-education knowledge tests. We also used the descriptive statistics (frequencies) for Morisky scale questionnaire scores. We compare the knowledge test result with the Morisky scale result. Median scores in the knowledge tests before and after the education program were compared using a paired samples Sign test. Also, the Chi-squared test was used to compare the percentage of patients who passed and failed before/after the education program. A P-value of less than 0.05 was considered to indicate a statistically significant difference.

For the Morisky 8-item scale, the scores for each response and the level of adherence score range as stated in the Cuevas et al. study was as follows; the questions with “no” response as a correct answer were questions number 1 through 7 except for question number 5 which was the only question with “yes” response as a correct answer. (175) The score results for each “no” response was rated as 1, and each “yes” response was rated as 0 except for question number 5, in which each “yes” response was rated as 1, and each “no” response was rated as 0. (175) As question number 8 was a 5-point Likert response and coded (0-4), it was standardized to be able to divide the result by 4 to calculate a summated score. (175) The answer with code 4 means the patient had a very good response, whereas the answer with code 0 means the patient had a very bad response.
4. DOACs pilot study

4.3.7. User feedback

Informal feedback on the DOAC education program was sought by email from the pharmacists who used the tool, and in the case of three hospital pharmacists specializing in anticoagulation, in person at a group interview. Owing to the small numbers involved, qualitative analysis was undertaken manually without specialist software, reviewing the pooled feedback to identify and extract common themes.
4.4. RESULTS

A total of 53 participants agreed to participate in the study, and all the patients completed the 20-item questionnaire in full with no missing answers. Also, all the participants completed a baseline Morisky 8-item questionnaire with no missing answers.

4.4.1. DOACs knowledge test result

The number of patients who passed the test before the education program was 43 (81.1%) patients and 10 (18.9%) failed the test (i.e. they answered less than 14 questions correctly, or more than 6 incorrectly. In contrast, The number of patients passed the knowledge test after the education program was 50 (94.3%) and only 3 (5.7%) patients failed. Six of the patients achieved a test score of 100% in the post-education test, while none of the patients achieved it in the pre-education test. See Figure 4.2.

![Figure 4.2: The number of DOAC patients who passed/failed in both pre-education test and post education test](image-url)
4.DOACs pilot study

The question which was most frequently answered correctly was question number 12: ‘While taking DOACs, which of the following represents a situation when you should go to the emergency room?’ (in case of emergency) with 100% (53/53) of patients answering correctly both before and after the education program and the correct answer was “you cough up blood”.

In contrast, the question which was least frequently answered correctly was question number 14: ‘while taking DOACs, you should call your anticoagulants clinic when you get:’ (adverse effects) with only 34% (18/53) patients answering correctly with “indigestion” before the program, while 43.4% (23/53) answering correctly after the program. (See Table 4.2.)

The questions showing the most improvement in knowledge after education were questions number 6, 8, and 13 with 100% (53/53) patients answering correctly in the second test. Question number 6 was ‘you have a cold, which includes a runny nose and cough. You—’ and the correct answer was “would call the anticoagulants clinic and tell him/her you are on DOACs medication and ask what you can take for your cold” with 86.8% (46/53) in the pre-education test, question number 8 was ‘when the need arises to take an antibiotic (to get rid of an infection) while taking DOACs you need to—’ and the correct answer was “call the anticoagulants clinic right away and let them know you are starting a new medication” with 94.3% (50/53) in the prior education test, and question number 13 was ‘your neighbour brings over this great (all natural) herbal supplement she just bought from her chiropractor. She swears that this helps all her aches and pains and recommends that you take it when you ache. your decision is  to—’ and the correct answer was “ask your pharmacist if the herbal supplement will interact with your medications before you take it” with 96.2% (51/53) in the first knowledge test.

In return, little improvement was seen for questions 5 ‘which of the following is an effect of DOACs medication that will most likely be experienced?’ with 49.1% (26/53) patients answering correctly “blood in the urine” in the second test compared with 28.3% (15/53) prior to education, and question 14 (less urgent effect) which was the least frequently answered correct question. (See Table 4.2.)

The questions showing no improvement in knowledge after the education program were questions number 4, 7, 9, and 18; for question number 4 (compliance with the dose and recommendations – action if the patient ran out of medicine) which 98.1% (52/53) of the patients answered correctly prior to education and after the education program and the correct answer was “call and ask for refills for that day so you do not miss a dose of DOAC”, questions number 7 (the action if the patient has a dental appointment) with 95.2% (51/53) of the patients answered correctly pre and post the education program and the correct answer was “must tell
your dentist you are taking DOACs well in advance of having any procedure done”, questions number 9 (compliance with the dose and recommendations – the best time of day to take DOACs) with 75.5% (40/53) of the patients answered correctly before and after the education program and the correct answer was “in the evening”, and number 18 (compliance with the dose and recommendations – action if the patient has generic and brand DOACs tablets with the same dose) with 90.6% (48/53) of the patients answered correctly in both the first and second test and the correct answer was “take only brand or generic, but not both”. (See Table 4.2.)

Two questions continued to be answered poorly (less than 50% of patients answered correctly) after the education program, namely questions 5, and 14. As the questions incorrect answered; for question number 5 was 15.1% (8/53) of the patients answered with “stroke”, 9.4% (5/53) of the patients answered with “leg clot”, and 26.4% (14/53) of the patients answered with “bruising”, while the correct answer was “blood in the urine”. For question number 14 was 3.8% (2/53) of patients answered with “backache”, 20.8% (11/53) of patients answered with “upset stomach”, 32.1% (17/53) of patients answered with “a tension headache”, while the correct answer was “indigestion”. See Table 4.2.
Table 4.2: Test results for each question before and after the DOACs education program

<table>
<thead>
<tr>
<th>Questions No.</th>
<th>Question topic</th>
<th>Number (%) of correct answers before the education program (n=56)</th>
<th>Number (%) of correct answers after the education program (n=56)</th>
<th>The most/ least frequently answered correctly</th>
<th>The most/ least improvement in knowledge after education</th>
<th>No improvement</th>
<th>Answered correctly by &lt; 50% of participants after education</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
<td>Suitable analgesics</td>
<td>40 (75.5%)</td>
<td>43 (81.1%)</td>
<td></td>
<td></td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Q2</td>
<td>Urgent treatment required</td>
<td>51 (96.2%)</td>
<td>52 (98.1%)</td>
<td></td>
<td></td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Q3</td>
<td>OTC multivitamin use</td>
<td>36 (67.9%)</td>
<td>50 (94.3%)</td>
<td></td>
<td></td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Q4</td>
<td>Running out of medicine</td>
<td>52 (98.1%)</td>
<td>52 (98.1%)</td>
<td></td>
<td>No improvement</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Q5</td>
<td>Common side effects</td>
<td>15 (28.3%)</td>
<td>26 (49.1%)</td>
<td></td>
<td>The least improvement in knowledge after education</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Q6</td>
<td>Treating a cold</td>
<td>46 (86.8%)</td>
<td>53 (100%)</td>
<td></td>
<td>The most improvement in knowledge after education</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Questions No.</td>
<td>Question topic</td>
<td>Number (%) of correct answers before the education program (n=56)</td>
<td>Number (%) of correct answers after the education program (n=56)</td>
<td>The most/ least frequently answered correctly</td>
<td>The most/ least improvement in knowledge after education</td>
<td>No improvement</td>
<td>Answered correctly by &lt; 50% of participants after education</td>
</tr>
<tr>
<td>---------------</td>
<td>------------------------------</td>
<td>-----------------------------------------------------------------</td>
<td>-----------------------------------------------------------------</td>
<td>---------------------------------------------</td>
<td>----------------------------------------------------------</td>
<td>----------------</td>
<td>----------------------------------------------------------</td>
</tr>
<tr>
<td>Q7</td>
<td>Informing the dentist</td>
<td>51 (95.2%)</td>
<td>51 (95.2%)</td>
<td></td>
<td>No improvement</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Q8</td>
<td>Antibiotics treatment</td>
<td>50 (94.3%)</td>
<td>53 (100%)</td>
<td>The most improvement in knowledge after education</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Q9</td>
<td>Dosage time</td>
<td>40 (75.5%)</td>
<td>40 (75.5%)</td>
<td></td>
<td>No improvement</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Q10</td>
<td>Sign of high INR</td>
<td>36 (67.9%)</td>
<td>43 (81.1%)</td>
<td></td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Q11</td>
<td>Interaction with drinks</td>
<td>19 (35.8%)</td>
<td>48 (90.6%)</td>
<td></td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Q12</td>
<td>Urgent treatment required 2</td>
<td>53 (100%)</td>
<td>53 (100%)</td>
<td>The most frequently answered correctly</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Q13</td>
<td>Herbal supplement interactions</td>
<td>51 (96.2%)</td>
<td>53 (100%)</td>
<td>The most improvement in knowledge after education</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Questions No.</td>
<td>Question topic</td>
<td>Number (%) of correct answers before the education program (n=56)</td>
<td>Number (%) of correct answers after the education program (n=56)</td>
<td>The most/least frequently answered correctly</td>
<td>The most/least improvement in knowledge after education</td>
<td>No improvement</td>
<td>Answered correctly by &lt;50% of participants after education</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------------------</td>
<td>---------------------------------------------------------------</td>
<td>---------------------------------------------------------------</td>
<td>---------------------------------------------</td>
<td>-----------------------------------------------------------</td>
<td>----------------</td>
<td>----------------------------------------------------------</td>
</tr>
<tr>
<td>Q14</td>
<td>Less urgent effect</td>
<td>18 (34.0%)</td>
<td>23 (43.4%)</td>
<td>The least frequently answered correctly</td>
<td>The least improvement in knowledge after education</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Q15</td>
<td>Monitoring</td>
<td>41 (77.4%)</td>
<td>46 (86.8%)</td>
<td>No</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q16</td>
<td>Factors influencing efficacy</td>
<td>47 (88.7%)</td>
<td>52 (98.1%)</td>
<td>No</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q17</td>
<td>Urgent treatment required 3</td>
<td>47 (88.7%)</td>
<td>52 (98.1%)</td>
<td>No</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q18</td>
<td>Use of generic</td>
<td>48 (90.6%)</td>
<td>48 (90.6%)</td>
<td>No improvement</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q19</td>
<td>Treatment duration</td>
<td>47 (88.7%)</td>
<td>50 (94.3%)</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q20</td>
<td>Risky activities</td>
<td>48 (90.6%)</td>
<td>52 (98.1%)</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4.4.2. Comparison of DOACs knowledge questionnaire scores before and after education

DOAC knowledge was found to improve in patients with a median score of 80% IQR (75-85) before the education program rising to 90% IQR (85-95) after the program. A paired samples sign test comparing percentage scores in the knowledge tests before and after education showed a highly significant improvement in scores ($Z = -6.645$, $P < 0.001$). Figure 4.3

Figure 4.3: Comparison of the correct scores in the knowledge test before and after education
4.DOACs pilot study

4.4.3. Influence of prior knowledge

The Chi-squared test was carried out to explore the proportions of patients passing/failing the knowledge test before/after the education program, and it was found to be highly statistically significant with \( P = 0.005 \). This result again indicates that there was a significant improvement in the patients' knowledge after the program. Figure 4.4

![Diagram showing proportion of patients passing/failing the knowledge test before/after the education program.](image)

**Figure 4.4: Proportion of patients passing/failing the knowledge test before/after the education program**

**\( P = 0.005 \) (indicate highly statistical significant)**
4. DOACs pilot study

4.4.4. Comparison of the percentage scores of warfarin and DOACs knowledge tests before and after the education program

By comparing the results of warfarin and DOACs knowledge tests, the question which was with 100% percentage before and after the education program in the both warfarin and DOACs test was question number 17 in warfarin test and 12 in DOACs test which was on ‘while taking your medicine, which of the following represents a situation when you should go to the emergency room?’ and the correct answer was “you cough up blood”. (See Table 4.3)

The questions with no improvement in both warfarin and DOACs knowledge tests were question number 8 in warfarin and 4 (running out of medicine) in DOACs with 98.2% and 98.1%, respectively and the correct answer was “call and ask for refills for that day so you do not miss a dose of DOAC”. Also, question number 14 in warfarin and 9 in DOACs (dosage time) with 98.2% and 75.5%, respectively and the correct answer was “in the evening”. (See Table 4.3)

The question which showed more improvement in DOACs patients compared to warfarin was question number 16 in warfarin and 11 in DOACs (interaction with drinks) with 33.9% and 33.8% before the education program, respectively and after the education program was 46.4% in warfarin and 90.6% in DOACs and the correct answer was “ensure nutritional supplement”. Moreover, question number 7 in warfarin and 3 in DOACs (OTC multivitamin use) with 67.9% both in pre-education test and in the second test was 83.95% in warfarin and 94.3% in DOACs and the correct answer was “purchase the multivitamin but do not start taking it until you have talked with the pharmacist at your Anticoagulant Clinic”. (See Table 4.3)

When comparing the percentages of the DOACs test with warfarin for the questions less frequently answered in DOACs than in warfarin were questions number 14 in warfarin and 9 in DOACs (dosage time) with 98.2% in both pre/post education test in warfarin and 75.5% in both pre/post education test in DOACs as mentioned before. In addition, question number 9 in warfarin and 5 in DOACs (common side effects) with 28.6% in warfarin and 28.3% in DOACs before the education program and after the education program the results were 60.7% in warfarin and 49.1% in DOACs and the correct answer was “blood in the urine”. (See Table 4.3)
## 4. DOACs pilot study

*Table 4.3: Comparison of knowledge test percentages before and after the education program for warfarin and DOACs.*

<table>
<thead>
<tr>
<th>Question number</th>
<th>Warfarin</th>
<th>DOACS</th>
<th>Question topic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-edu-</td>
<td>Post-</td>
<td>Pre-edu-</td>
</tr>
<tr>
<td></td>
<td>cation</td>
<td>education</td>
<td>cation</td>
</tr>
<tr>
<td>Q1</td>
<td>85.7%</td>
<td>92.9%</td>
<td>Q1</td>
</tr>
<tr>
<td>Q3</td>
<td>89.3%</td>
<td>96.4%</td>
<td>Q2</td>
</tr>
<tr>
<td>Q7</td>
<td>67.9%</td>
<td>83.9%</td>
<td>Q3</td>
</tr>
<tr>
<td>Q8</td>
<td>98.2%</td>
<td>98.2%</td>
<td>Q4</td>
</tr>
<tr>
<td>Q9</td>
<td>28.6%</td>
<td>60.7%</td>
<td>Q5</td>
</tr>
<tr>
<td>Q10</td>
<td>83.9%</td>
<td>96.4%</td>
<td>Q6</td>
</tr>
<tr>
<td>Q11</td>
<td>96.4%</td>
<td>98.2%</td>
<td>Q7</td>
</tr>
<tr>
<td>Q12</td>
<td>92.9%</td>
<td>96.4%</td>
<td>Q8</td>
</tr>
<tr>
<td>Q14</td>
<td>98.2%</td>
<td>98.2%</td>
<td>Q9</td>
</tr>
<tr>
<td>Q15</td>
<td>67.9%</td>
<td>80.4%</td>
<td>Q10</td>
</tr>
<tr>
<td>Q16</td>
<td>33.9%</td>
<td>46.4%</td>
<td>Q11</td>
</tr>
<tr>
<td>Q17</td>
<td>100%</td>
<td>100%</td>
<td>Q12</td>
</tr>
<tr>
<td>Q18</td>
<td>96.4%</td>
<td>98.2%</td>
<td>Q13</td>
</tr>
<tr>
<td>Q21</td>
<td>42.9%</td>
<td>55.4%</td>
<td>Q14</td>
</tr>
</tbody>
</table>
### 4.DOACs pilot study

<table>
<thead>
<tr>
<th>Question number</th>
<th>Warfarin Pre-education percentage</th>
<th>Warfarin Post-education percentage</th>
<th>DOACS Pre-education percentage</th>
<th>DOACS Post-education percentage</th>
<th>Question topic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q22</td>
<td>87.5%</td>
<td>96.4%</td>
<td>Q15</td>
<td>77.4%</td>
<td>Monitoring</td>
</tr>
<tr>
<td>Q23</td>
<td>85.7%</td>
<td>96.4%</td>
<td>Q16</td>
<td>88.7%</td>
<td>Factors influencing efficacy</td>
</tr>
<tr>
<td>Q24</td>
<td>80.4%</td>
<td>87.5%</td>
<td>Q17</td>
<td>88.7%</td>
<td>Urgent treatment required 3</td>
</tr>
<tr>
<td>Q26</td>
<td>85.7%</td>
<td>91.1%</td>
<td>Q18</td>
<td>90.6%</td>
<td>Use of generic</td>
</tr>
<tr>
<td>Q28</td>
<td>91.1%</td>
<td>96.4%</td>
<td>Q19</td>
<td>88.7%</td>
<td>Treatment duration</td>
</tr>
<tr>
<td>Q29</td>
<td>94.6%</td>
<td>98.2%</td>
<td>Q20</td>
<td>90.6%</td>
<td>Risky activities</td>
</tr>
</tbody>
</table>
4. DOACs pilot study

4.4.5. Differences in the scores of DOACs patients test if we excluded question number 9 (dosage time) result

Due to the fact patients daily regimen may vary from patient to patient, and that test answer options were not suitable for twice daily regimen patients; when we excluded this question (dosage time) from the result the number of patients who passed the test pre- and post the education test were 39 (73.6%) and 48 (90.6%), respectively. However, the number of patients who failed increased to 14 (26.4%) in the pre-education test and only 5 (9.4%) of the patients in the post-education test.

4.4.6. Morisky 8-item scale results

All patients completed the baseline Morisky 8-items scale questionnaire without any missing responses. The Morisky 8-items scale adherence questionnaire was found to be high in patients at the baseline with a median score 7 IQR (7-8) and the result of total responses for each question shown in Table 4.4.
Table 4.4: The total responses for Morisky scale questionnaire

<table>
<thead>
<tr>
<th>Question number</th>
<th>Number of patients’ answered with (Yes)</th>
<th>Number of patients’ answered with (No)</th>
<th>The correct response</th>
<th>Question topic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
<td>4</td>
<td>49</td>
<td>No</td>
<td>Forget sometimes to take your medicine</td>
</tr>
<tr>
<td>Q2</td>
<td>1</td>
<td>52</td>
<td>No</td>
<td>Over the past 2 weeks, any days you did not take your medicine</td>
</tr>
<tr>
<td>Q3</td>
<td>-</td>
<td>53</td>
<td>No</td>
<td>In case of feeling worse you cut back or stopped taking your medication without telling your doctor</td>
</tr>
<tr>
<td>Q4</td>
<td>2</td>
<td>51</td>
<td>No</td>
<td>Forget to take the medicine in case of travel or leave home</td>
</tr>
<tr>
<td>Q5</td>
<td>53</td>
<td>-</td>
<td>Yes</td>
<td>Dosage of yesterday</td>
</tr>
<tr>
<td>Q6</td>
<td>-</td>
<td>53</td>
<td>No</td>
<td>Fin case if you feeling your condition is under control, and stop taking your medicine</td>
</tr>
<tr>
<td>Q7</td>
<td>21</td>
<td>32</td>
<td>No</td>
<td>feeling hassled about sticking to your DOACs medicine</td>
</tr>
</tbody>
</table>
The result for question number 8 “how often do you have difficulty remembering to take all your blood pressure medication?”; see Table 4.5 for the results for each option as only 9 answered with “never/rarely” which is the best response and only one of the total 53 patients answered with “all the times” which is the worst response.

*The best response was number 4 and the worse response was number 0

The total scores on the MMAS-8 items questionnaire ranged from 0 to 8, in which scores of 8 indicated that the patient had high adherence, 7 or 6 indicated medium adherence, and <6 indicated low adherence. (175) Most of the patients had medium to high adherence to their DOACs medicine, as shown in Table 4.6.

*Table 4.6: Adherence levels for Morisky 8-items scale result among DOAC patients*
4.4.7. Comparison of the pre-knowledge test result with the Morisky 8-item scale result

When tested before undertaking the education programme, the median scores obtained by patients with low, medium and high adherence were 85%, 80% and 85% respectively, and the p-value was <0.001. However, it should be noted that the numbers were small, particularly in the low adherence group (only 4 patients), giving rise to the likelihood that these may not have been representative of the wider patient population.
4.DOACs pilot study

4.5. DISCUSSION

4.5.1. DOACs knowledge test result

The findings of this pilot study showed that 50 of the total 53 patients (94.3%) passed the knowledge test after the electronic education program. This high percentage suggests that the education tool is suitable for a more comprehensive study with a larger sample size. In addition, to our knowledge this is the first study in Ireland appraising an electronic counselling tool providing information on DOACs and evaluating patients’ knowledge on their DOAC medication.

Question number 14 (less urgent effect) was the least frequently answered correctly, and one of the two questions in which less than 50% of patients answered correctly and was also the question showing least improvement along with question number 5 (common side effects).

The reason for this low score in question number 14, where the correct answer was indigestion, is probably because the education programme did not focus specifically on this point. This was because we wanted to make the electronic program easy, including the important information that patients need without overwhelming them. Therefore, we did not add a section for the less urgent effects in the electronic program, but instead we prioritized the most common side effects which related to bleeding. In addition, we added information about how to take the dose, and this information related about how to overcome this side effect (dabigatran should be taken with food to prevent stomach upset, apixaban can be taken with or without food, rivaroxaban and edoxaban must be taken with or after a meal). In the future, we will modulate the version of the DOACs electronic program to include this in a more obvious way, for example; adding a picture that shows the person having stomach pain because he/she took medicine before food.

For the question concerning the most likely side effects to be experienced (question number 5), with the correct answer being blood in the urine, this information was mentioned in the program under the side effects section which focused on triggers for the patient going directly to the emergency room. Patients’ lack of recollection of this information may be because it appeared in the voiceover only as a conversation between the pharmacist and the patient, and in view of patients’ likely different learning styles, this single format was not enough. In this case, if we add a small part of the video that reinforces these situations through pictures, it will be more accessible to the patients, facilitating retention of this information.

The questions which achieved 100% score after the education program were: questions number 6 (treating a cold), number 8 (antibiotics treatment), and number 13 (herbal supplement interactions). The information in the education program was very obvious that the patients
should check with their doctor or pharmacist before taking any other medication, including herbal remedies, multivitamins, or over the counter medications. This result for these questions reflecting that the electronic education program works effectively with this type of scenario.

Questions number 4 (running out of medicine), number 7 (informing the dentist), number 9 (dosage time), and number 18 (use of generic) were the questions with no improvement results in the knowledge after the education program. Even without improvement for questions number 4, 7, and 18, patients’ overall results were over 90% meaning most of them had good knowledge, leaving less scope for improvement. Except for question number 9, the result was 75.5% before and after the education program as the information in the program was general (you should take your medicine at the same time each day), so the patients probably answered according to their daily habit of taking their DOAC medicine.

4.5.2. Comparison of the percentage scores of warfarin and DOACs patients before and after the education program

According to the advantages of DOACS over warfarin mentioned in the introduction (chapter 1 section 1.3.9), DOACs have a clear benefit in reducing intracranial bleeding and offer a more convenient therapy for patients. (176) Although VKAs are still the preferred anticoagulants in some cases, physicians should also look at reasons to use DOACs, instead of searching for reasons to avoid using them. (176) Furthermore, they should help in ensuring that more eligible AF patients receive an appropriate anticoagulant therapy based on their stroke and bleeding risks, as the switching strategies vary depending on which drug the physician chooses for the patient and the in target INR. (176)

One systematic review and meta-analysis reported that DOACs were a safe and effective alternative for warfarin in the prevention of stroke and systemic embolism in AF patients and in risk factors for stroke. In addition, they reported a reduction in intracranial bleeding, which leads to significantly lower mortality. (177) The intracranial bleeding risk is 52% lower with DOACs compared to warfarin, with extremes ranging from 33 to 70%. (178) Another study by Yao et al. has reported similar findings regarding safety and efficacy of DOACs, and this evidence may facilitate clinical decision making. (179) Nonetheless, the choice between DOACs and warfarin will depend on each patient’s risk and preference. (179) Nowadays, many of patients are switched from warfarin to DOACs. The advent of the DOACs established a new era for anticoagulation therapy and the counselling regarding these medications that is required.
When the scores in the warfarin knowledge test were compared to those in the DOAC knowledge test, the questions concerning running out of medicine and dosage time showed no improvement in either the warfarin or the DOAC knowledge test. However, the scores for the question regarding running out of medicine were high in both warfarin and DOAC knowledge tests, and this may be due to previous emphasis from their care providers to patients about the risks associated with not taking medicines in general.

On the other hand, the question relating to the dosage time, the scores were higher in the warfarin knowledge test compared to the DOAC knowledge test, with no improvement after the education program. The reason for this result may be due to warfarin patients being careful about their dosage time because they know the bleeding risk associated with warfarin is very high and that warfarin is a high alert medication, while DOAC patients were either new to the drug or they switched to it. Moreover, there is a possibility that those patients answered correctly but because the questions options restricted to once daily dose as in which they may be had various possible dosage regimen like if they were on a twice-daily regimen. In this case, we need to modify this question to be suitable for those patients with multiple daily dosages.

For two questions, higher scores were attained in the DOAC knowledge tests than in the warfarin test. These were regarding interaction with drinks and OTC multivitamin use. In the warfarin electronic program, the information about the food-drug interactions was general and contained detailed information about food/multivitamin-drug interactions. Whereas in the DOAC electronic program, the information on multivitamin-drug interactions was clear and concise: There was a specific statement that “you should check with your doctor or pharmacist before taking any other medication, including herbal remedies, multivitamins, or over the counter medications”. It is probable that this is the reason why patients easily recalled the information from the DOAC electronic program more than the information in the warfarin electronic program.

In contrast, for two other questions, higher scores were attained in the warfarin knowledge tests than in the DOAC tests. These questions were regarding dosage time (possible reasons for which have previously been discussed) and common side effects. The patients on warfarin were not new start patients, and may have been counselled many times and very precisely regarding the warfarin benefits and risks by their physicians and pharmacists. However, the DOAC patients included patients who were newly on DOACs, or those who may have switched to DOACs under the recommendation of their physician, and they needed time to be familiar with information.
on these drugs. For this reason, our electronic program was designed for patients to repeatedly use at any time.

4.5.3. Morisky 8-item scale results

The purpose of this educational program was not only to reinforce the medical information provided to the patients, but it was also to motivate them to adhere to their medication and reduce the complications potentially associated with misunderstanding and misuse.

Patients in this study reported a good response to the questions from 1 through 6 except question number 7 (feeling hassled about sticking to your DOAC) and number 8 (difficulty in remembering the DOAC). This result was not surprising as it is possible for patients, even if they keep taking their medication, to have uncomfortable and frustrating feelings about taking their medication and to encounter difficult times when it was an effort to remember to take their medicine.

However, most of the patients had Morisky 8-item scale results ranging between the medium (23/53) and high level of adherence (26/53), while only four of them had a low level of adherence. This result indicated that overall the patients had good adherence to DOACs. In contrast to our finding, one Turkish study on drug adherence using the Morisky 8-item scale in patients with nonvalvular AF taking DOACs found that adherence of the Turkish population to DOACs was quite low (<50%), and they reported that the reasons concerning this result of the low level of adherence were associated with bleeding and thromboembolic events, education level, sociocultural status, the number of drugs, taking the dose twice a day, having more than one disease and information about their diseases, and psychiatric disorders. (180) As well, they recommended that the risk factors particular to a patient should be evaluated, and the clinical and educational processes should be coordinated to improve medication adherence. (180) Likewise, one American study on older adult patients using a warfarin app to improve the patients’ knowledge utilized the Morisky 8-item scale to evaluate adherence. However, it did not report the patients’ actual levels of adherence, but instead just indicated that there was no significant change in adherence over the course of the study. (136)

Because this study was a pilot study and the duration was short, we could not assess the patients’ adherence after the education program. also, when we compared the pre-education test with adherence level for each group, we found that the low adherent patient group had the same level of knowledge compared to the high adherence group. This result may not be representative of the wider population and we cannot depend on it because the patient
4.DOACs pilot study

numbers in the low adherence group were very small (only four), while the high adherence group contained 26 patients.

4.5.4. Additional support

Patient education alone may not be enough for patients to overcome the difficulties that they face during their daily life that hinder effective treatment: For example, even with comprehensive education, patients may have difficulty remembering the dosage time in cases of polypharmacy, or those with cognitive impairment or dementia. Therefore additional support from pharmacists, physicians, and caregivers may be required to help these patients to improve their adherence, minimize complications, and improve clinical outcomes. In addition to this support and education, the use of a reminders tool (e.g. a pill box, or monitored dose system) or using electronic pill reminder and medication tracker apps on mobile devices could be helpful, for example; the Mango health app and MediSafe app. (181, 182) These electronic medication reminder apps may have several features including education about drug information, a drug interaction reminder when you add multiple drugs, refill reminder, and the opportunity to share information from the app with health care providers, family, or a friend in case of help.
4.6. USER FEEDBACK

Feedback on the DOAC education program was provided by the pharmacists who used it with their patients (incorporating feedback from the patients themselves) as well as by three pharmacists specializing in anticoagulation.

As for the warfarin program, users found favour with the DOAC education tool:

- “Thanks for the opportunity to try this out. I really liked it. I’d be interested in any updates.” [Pharmacist 2]
- “I don’t think I counsel on these [the DOACs] as much as I should compared to warfarin, so this was a help.” [Pharmacist 8]

However, also as before there were suggestions for improvement relating to content, format and navigation.

Content

Some users felt the level of information was pitched at the right level:

- “Just the right amount of info.” [Pharmacist 5]
- “Good balance of time vs information.” [Pharmacist 3]

However, a wish for more information on the underlying circumstances leading to anticoagulation was also expressed:

- “A lot of our patients don’t have a good understanding of why they’ve been prescribed an anticoagulant, and the background here was very general. Could there be something more specific for different groups of patients?” [Pharmacist 4]

This concept was discussed further with hospital pharmacists specializing in anticoagulation and it was considered desirable to have multiple versions of the educational program, a suitable version being selected by the pharmacist for the patient depending on his/her personal circumstances (medical condition, drug, dose, age, gender etc.) so that each would get a personalized set of information (to a greater extent than in the pilot program).

A version without any personalization, giving high level information suitable to all patients, was also proposed for playing on a monitor in the hospital anticoagulation clinic.

Format

The dialogue format was considered to work well:
4. DOACs pilot study

- “Conversation between patient and pharmacist was good – nice way to give info.” [Pharmacist 5]
- “Positives: Conversation style – made learning informal.” [Pharmacist 3]

The graphics were considered to match the hospital anticoagulation clinic environment well, but some pharmacists expressed the view that it would also be nice to have versions that showed a bedside consultation or a community pharmacy consultation, so as to align more closely with their patients’ experience. In this regard, they also mentioned having a range of patient avatars with different demographic profiles (age, gender etc.) so that patients could potentially identify more closely with the person being counselled in the program.

Navigation

The main issue raised about navigation was the need in the pilot program for patients to select the drug they were using, as some of the content differed from drug to drug. Pharmacists indicated that in a number of instances they had intervened to assist their patients at this point, and it was considered preferable to have all such decision points at the start of the program so that they could be selected by the pharmacist before the patient began the program, and locked in so that these preferences would remain if the patient later accessed the program on their own to reinforce their knowledge.
4.7. CONCLUSION

Technology-based educational interventions these days are becoming more advanced and the growing market of smartphones, tablets, and smartwatches, has encouraged the use of electronic education interventions, as many scientists and medical companies have been interested in developing programs, applications, and websites that help patients to improve their health. These interventions contain the information about the medication in a motivational, easy and attractive way to encourage patients to use them. The goal of our study was to pilot our interactive electronic program that may be used in future to help DOAC patients to achieve good compliance with their medication and enhance their drug knowledge, in order to improve clinical outcomes and decrease the complications associated with drug use. For that reason, future studies will focus on measuring the effectiveness of this intervention on clinical outcomes.

This type of intervention helps reduce pharmacist time needed for counselling and hence has the potential to facilitate a busy clinic or other healthcare environment to meet its educational goals as demonstrated by Moore et al. and Denizard-Thompson et al. (130, 137). In future work, the need to measure whether our intervention will help healthcare providers to decrease the time for counselling while still providing a professional health service for patients.

This pilot study found that the electronic education program shows a favourable result as regards patient knowledge improvement, and this result is encouraging for future assessment of this intervention in a large sample size with more comprehensive measurement tools and outcomes.
4. DOACs pilot study
5. Overall Findings

5.1. STRENGTHS AND LIMITATIONS

The strength in this thesis that the systematic review was the first review assessing the effectiveness of the electronic education program for warfarin patients and represents a complete examination of the literature to date. However, the limitations of this systematic review were the small number of published studies meaning that only four studies were included, with small sample sizes, and these were heterogeneous which led to limitations on our conclusions.

A strength regarding the electronic education tool studies, were that these tools were found useful even when the sample size was small, in diverse settings (community and hospital practice). While larger numbers will be recruited in the future comprehensive trial, the current studies were purely pilot studies and their purpose was to assess the feasibility and the process of the electronic education tools.

The Morisky 8-item scale was used as a measurement tool in this study because this tool was reported to have higher validity and reliability in patients with chronic diseases without disadvantages compared to the other self-reported questionnaire and scales. (85) In one systematic review, the Morisky 8-item scale was the only validated measurement tool for warfarin. (183) However, despite this previous validation, we found that the Morisky 8-item scale did not focus on adherence involving overuse; it only focused on underuse adherence, a limitation which we detected in our pilot study. For oral anticoagulants, both types of non-adherence is necessary to detect, as their underuse causes thromboembolism, while overuse causes bleeding. For future studies, we suggest that a new, validated adherence measurement tool will be required to cover both the underuse and the overuse adherence questions, for example; the tools should considered also questions related to overuse like “When you feel like your condition is not under control, do you sometimes take more of your medicine?”. This demonstrates the importance of our pilot work. Moreover, a previous cross-sectional survey suggested adding two questions to investigate if the patient took warfarin at a regular time each day and if the patient took the dosage exactly as prescribed because both regular timing and appropriate dosage are critical to anticoagulation control. (184)
5.2. FUTURE WORK

5.2.1. Protocol for DOAC electronic education program ongoing study

5.2.1.1. Study design and setting

Randomized controlled trial conducted in the pharmacist-led outpatient anticoagulation clinics in hospital.

5.2.1.2. Participants in the study

All patients who receive DOACs, are over 18 years old, can speak and read English, and who can use electronic devices (smartphone, iPad, tablet, or laptop) will be included in the study. We will exclude patients who are children (under 18 years), are blind, have cognitive impairment or dementia, those who are pregnant, or patients unable to speak or read English.

Informed consent will be obtained for all patients before they are exposed to the electronic program of DOAC counselling.

A computer-generated list of random numbers (Microsoft Excel) will be used to assign the patients to either the intervention group or the control group. Patients in the intervention group will be educated by a new electronic program for DOACs according to their prescription, while the control group will receive usual care carried out by the pharmacists in the outpatient clinic. Because the nature of the intervention it will not be possible for patients and staff to be blinded throughout. However, blinding of participants will be maintained until after their enrolment. Hence the patients will be blinded to the allocation, but not blinded to the intervention.

The patients’ knowledge will be measured using a newly validated anticoagulant knowledge assessment test, consisting of a 20-item questionnaire, developed with minor modifications from the AKA test to accommodate the specific characteristics of the DOACs. Both groups will undertake the knowledge test before education (baseline) and immediately after they receive their education (post-counselling), then after three months, six months, and 12 months follow-up.

Also, the patients’ adherence will be measured using a newly validated tool developed an extension of the Morisky 8-item adherence scale, with both groups undertaking the adherence test before education (baseline) and then three months, six months, and 12 months after they received their education (post-counselling).
5. Overall findings

5.2.1.3. Intervention development and modification

The development of the DOAC electronic education program has previously been described in the electronic counselling for oral anticoagulants patients, DOACs pilot study (chapter 4 section 4.1.3).

The modifications required for the education program according to the recommendation of Tallaght hospital pharmacists, and the pilot study results were:

- Adding a version specifically for AF patients as part of the education program.
- Adding more options to personalize the program for individual patients according to age (under 18, 18-30, 31-50, over 50 years old), sex (male, and female), having AF or not, and the type of DOAC medication.
- The pharmacist has the control at the outset to press the options for each patient according to their situation, so each patient will have his/her specific information depending on their age, sex, AF status, and the DOAC type.
- With respect to the dosage time question, we will modulate the question to be suitable for each patient’s dosage regimen (i.e. different for each DOAC) as the pharmacist can choose from the beginning what is the patient’s daily dosage regimen. The question options and the answer deemed to be correct will then appear according to what the pharmacist has chosen, in a tailored manner for each patient.
- The pharmacist should be able to see the final result for each patient, so they can do fast additional counselling for the patient regarding each weak point. This way of education will help the pharmacist to improve pharmacy services and reduce the time spent for counselling.

5.2.1.4. The knowledge test questionnaire and adherence test questionnaire modifications

Because of the wide use of the AKA test to measure the improvement in patient knowledge and the Morisky 8-item scale as a medication adherence measurement tool, we were interested in using them in our pilot study to facilitate comparisons with the published literature. However, we found some disadvantages regarding using these tests, thus to use them in the future, more comprehensive study, we will make modifications, taking into consideration they should be close as possible to the original tests and at the same time suitable for DOAC patients’ requirements and allow us to easily compare our result with the results of the other studies. In this case, we will modulate both tests, and then we will trial them separately to ensure the validity and reliability of both tests before using them in our future study. In the AKA knowledge
5. Overall findings

test we will change the options of question number 9 as we mentioned above, while in the adaptation of the Morisky 8-item scale, we will add extra questions related to overuse, dosage time and appropriate dosage to cover all the topics of DOAC medication adherence types.

5.2.1.5. Study outcomes

Primary outcome

Improvement of patients’ knowledge as demonstrated in the pre-education test and post-education test (having previously validated the new knowledge test). The passing score for the test will be 70%, as shown previously according to our calculation in the DOAC pilot study (Chapter 4: Electronic Counselling for Oral Anticoagulants Patients).

Secondary outcomes

Adherence to treatment (having previously validated the new adherence questionnaire). Clinical outcomes: Clinical measures of anticoagulant efficacy, and adverse event incidence. The difference in pharmacist time spent counselling between the electronic education group and usual care group (total time).

5.2.1.6. Sample size and statistical analysis

The quantitative data collected from the Articulate 360 software will be analysed by using the software IBM Statistical Package for the Social Sciences (SPSS) statistics version 25.0 (IBM Analytics, New York, USA) and Microsoft Excel software, version 16.14.03 (Microsoft Corporation, Washington, USA). In SPSS, we will use descriptive statistics (frequencies) for the 20 questions to compare the percentage of correct answers in tests before and after undertaking the education programme, to find the questions most frequently answered correctly and incorrectly, questions in which there was the most improvement, the least improvement, and the questions that were still answered poorly (< 50% of respondents) after the education program.

The passing score will be used to determine how many patients passed and how many failed in both the pre-education and post-education knowledge tests. We will also use the descriptive statistics (frequencies) for the adherence scale questionnaire scores. Potential interrelationships will be explored between the knowledge test result and the adherence scale result. Median scores in the knowledge tests before and after the education program will be compared using a paired samples Sign test. Also, the Chi-squared test will be used to compare the percentage of
5. Overall findings

patients who passed and failed before/after the education program. A P-value of less than 0.05 will be considered to indicate a statistically significant difference.

The required sample size has been calculated to detect a 15% improvement in knowledge. According to the research of Wang et al., we need a minimum of 73 patients per group. (185) However, to ensure confidence and to allow for 20% attrition, we intend to recruit a minimum of 88 patients per study group, so the expected total minimum number will be 176 patients. These will be randomized in a 50:50 ratio to the two groups (intervention and usual care group).
5. Overall findings

5.3. OVERALL CONCLUSION

The systematic review revealed that previous work in this area comprises a diverse and small number of studies. The educational interventions in those studies generally demonstrated positive effects for electronic counselling but the evidence is rather weak. The broad implication of the present thesis is that we successfully developed and piloted tools for educating patients on warfarin and DOACs. We have shown that the participants' knowledge improved for both warfarin and DOACs in the short term. We also identified refinements for these tools in order to improve their suitability in clinical practice.

Overall, the work described in this thesis lays the foundation for conducting a comprehensive randomized controlled trial to definitively evaluate the impact of such tools on a range of clinical and non-clinical (e.g. time management) parameters, to guide future pharmacy practice.


References


References


References


References


References


References


References


References


Appendices
Appendix 1

The 8-Item Morisky Medication Adherence Scale: (93)

1. Do you sometimes forget to take your high blood pressure pills?

2. Over the past 2 weeks, were there any days when you did not take your high blood pressure medicine?

3. Have you ever cut back or stopped taking your medication without telling your doctor because you felt worse when you took it?

4. When you travel or leave home, do you sometimes forget to bring along your medications?

5. Did you take your high blood pressure medicine yesterday?

6. When you feel like your blood pressure is under control, do you sometimes stop taking your medicine?

7. Taking medication everyday is a real inconvenience for some people. Do you ever feel hassled about sticking to your blood pressure treatment plan?

8. How often do you have difficulty remembering to take all your blood pressure medication?
Appendices
Appendix 2

The original AKA instrument (correct answers indicated with *) (102)

1. Which one of these medications is recommended if you are taking Coumadin (warfarin) and want relief from a headache?
   a. Advil.
   b. Motrin.
   c. Aspirin.
   d. Tylenol.*

2. Which of the following food items would interfere with your Coumadin (warfarin) medication?
   a. Bacon.
   b. Broccoli.*
   c. Bananas.
   d. Peeled cucumbers.

3. While on Coumadin (warfarin) medication, in which of the following would you go directly to the emergency room?
   a. Small bruises.
   b. Your appetite dramatically increases.
   c. Nosebleed which will not stop bleeding.*
   d. Gums which bleed for a few seconds after brushing teeth.

4. You just remembered that you forgot to take your evening Coumadin (warfarin) medication dose last night. You would---
Appendices

a. skip the dose of Coumadin (warfarin) you missed.*

b. take the missed Coumadin (warfarin) dose right now.

c. wait and take 2 doses of Coumadin (warfarin) this evening.

d. take one-half of the missed dose of Coumadin (warfarin) right now.

5. While on Coumadin (warfarin) you ---

a. should not eat spinach.

b. can eat spinach one time a month.

c. can eat as much spinach as you would like whenever you would like.

d. can eat spinach but need to eat the same amount regularly every week.*

6. While out with friends for dinner, you have just finished your third glass of wine. This amount of alcohol consumed in a single evening will---

a. cause a decrease in your INR.

b. cause an increase in your INR.*

c. not affect you or your Coumadin (warfarin) in any way.

d. make you sick when taking Coumadin (warfarin) medication.

7. While in your pharmacy, you notice multivitamins are on sale. After some thought, you decide that you may need a multivitamin. You would---

a. purchase the multivitamin and begin taking it regularly.

b. not take a multivitamin because it will cause a blood clot while taking Coumadin (warfarin).

c. start taking it and bring the multivitamin to your next Coumadin Clinic visit to show the pharmacist.
Appendices

d. purchase the multivitamin but not start taking it until you talked with the pharmacist at your Coumadin Clinic.*

8. If you ran out of your prescription for your Coumadin (warfarin) you would---

a. borrow Coumadin (warfarin) from a friend, as long as it is the same dose as yours.

b. call and ask for refills for that day so you do not miss a dose of Coumadin (warfarin).*

c. wait until your next appointment that is just a few days away to get a new prescription.

d. do nothing because you have taken Coumadin (warfarin) long enough, otherwise there would be more refills on your prescription.

9. Which of the following is an effect of Coumadin (warfarin) medication that will most likely be experienced?

a. Stroke.

b. Leg clot.

c. Bruising.*

d. Blood in the urine.

10. You have a cold, which includes a runny nose and a cough. You---

a. could safely take Nyquil to help get rid of the runny nose and cough.

b. take your friend’s medication that he/she uses for a bad cold because he/she is also on Coumadin (warfarin) medication.

c. would call the Coumadin Clinic and tell him/her you are on Coumadin (warfarin) medication and ask what you can take for your cold.*

d. decide it is safer to suffer through the cold because most cold medications will interact with your Coumadin (warfarin) medication.
Appendices

11. When making a dental appointment while taking Coumadin (warfarin) medication, you need to remember you---

a. cannot have procedures done on your teeth while taking Coumadin (warfarin).

b. must tell your dentist you are taking Coumadin (warfarin) well in advance of having any procedure done.*

c. can have procedures done and there is not a need to tell the dentist about the Coumadin (warfarin).

d. can have the dental procedure done if when you arrive at your dental appointment you tell the dentist you are taking Coumadin (warfarin).

12. When the need arises to take an antibiotic (to get rid of an infection) while taking Coumadin (warfarin), you need to---

a. take half of the prescribed length of therapy, and then call the Coumadin Clinic.

b. refuse to take any new medication because you are taking Coumadin (warfarin).

c. wait until your next Coumadin Clinic visit and then tell the pharmacist about the antibiotic.

d. call the Coumadin Clinic right away and let them know you are starting a new medication.*

13. Coumadin (warfarin) works---

a. in my liver to make my blood thicker.

b. in my liver to make my blood thinner.*

c. in my kidneys to make my blood thicker.
d. in my kidneys to make my blood thinner.

14. The best time of day for me to take my Coumadin (warfarin) is ---

a. at lunchtime

b. in the evening.*

c. in the morning before breakfast.

d. any time of day when I remember.

15. Which of the following is an effect of my Coumadin (warfarin) medication that I will most likely experience if my INR is too high?

a. A clot in the leg.

b. Minor bleeding.*

c. Clot in the lung.

d. Bleeding in the brain.

16. Which of the following drinks can decrease the effectiveness of your Coumadin (warfarin)?

a. Deans 2% low-fat milk.

b. Hershey’s chocolate shake.

c. Tropicana orange juice.

d. Ensure nutritional supplement.*

17. While taking Coumadin (warfarin), which of the following represents a situation when you should go to the emergency room?

a. You cough up blood.*

b. Your nose bleeds slightly while blowing it.
c. You gums bleed after brushing your teeth then it stops quickly.

d. You have cut yourself while shaving and you control the bleeding.

18. Your neighbor brings over this great “all natural” herbal supplement she just bought from her chiropractor. She swears that this helps all her aches and pains and recommends that you take it when you ache. Your decision is to---

a. take her advice, realizing that you could use this herbal supplement.

b. start taking the herbal supplement and tell your pharmacist at the next office visit.

c. ask your pharmacist if the herbal supplement will interact with your medications before you take it.*

d. avoid taking herbal supplements altogether because all medications interact with Coumadin (warfarin).

19. Once you have reached a stable Coumadin (warfarin) dose, a PT/INR blood test---

a. should be checked once a year.

b. should be checked once every 3 months.

c. should be checked at least once every 4 weeks.*

d. does not need to be checked once you are on a stable Coumadin (warfarin) dose.

20. The results of your PT/INR test tells the pharmacist---

a. how thick or thin your blood is while taking Coumadin (warfarin).*

b. how well your kidneys are working since taking Coumadin (warfarin).

c. what your average blood sugar level was since taking Coumadin (warfarin).

d. how much alcohol you have been drinking since taking Coumadin
21. While taking Coumadin (warfarin), you should call your Coumadin Clinic when you get:

a. a backache.
b. an upset stomach.
c. a tension headache.
d. diarrhea for more than 1 day.*

22. While on Coumadin (warfarin) you need to be routinely monitored for which of the following:

a. PT/INR tests.*
b. Potassium levels.
c. Blood glucose levels.
d. Kidney function tests.

23. Which of the following may have a significant effect on how well your Coumadin (warfarin) works?

a. Changes in your mood.
b. Changes in sleep habits.
c. How much water you drink.
d. Using over the counter medications.*

24. While taking Coumadin (warfarin), which of the following should lead you to the emergency room?

a. Loss of appetite.
b. Brown loose stools.
Appendices

c. Urine becomes red in color.*

d. A quarter size bruise on your arm.

25. Which of the following foods could affect how well your Coumadin (warfarin) works?

a. Celery.

b. Carrots.

c. Cole slaw.*

d. Green beans.

26. You have generic and brand Coumadin (warfarin) tablets at home that are both the same dose. You should

a. take both because they work differently.

b. take only brand or only generic, but not both.*

c. not take either until you call the Coumadin Clinic.

d. alternate days by taking brand on one day and generic on the next day.

27. Once your Coumadin (warfarin) is stopped, how long does it take to get the medication to get out of your system?

a. 5 hours.

b. 5 days.*

c. 5 weeks.

d. 5 months.

28. After starting Coumadin (warfarin), how long (in months/years) would you expect to be taking Coumadin (warfarin)?
a. 1 year.

b. 1 month.

c. It depends on each person’s needs.*

d. If you start Coumadin (warfarin), you will have to be on the medication for the rest of your life.

29. Which of the following activities are more risky while taking Coumadin (warfarin)?

a. Playing football, because you can hit your head.*

b. Taking a bath, because soap interacts with Coumadin (warfarin).

c. Playing cards because using your hands a lot will cause a blood clot.

d. Walking a lot, because exercise is not good for you while taking Coumadin (warfarin).
Appendix 3

DOACs knowledge test (correct answers indicated with *)

1. Which one of these medications is recommended if you are taking DOACs and want relief from a headache?
   A. Panadol. *
   B. Disprin.
   C. Buplex.
   D. Nurofen.

2. While on DOAC medication, in which of the following would you go directly to the emergency room?
   A. Small bruises.
   B. Your appetite dramatically increases.
   C. Nosebleed which will not stop bleeding. *
   D. Gums which bleed for a few seconds after brushing teeth.

3. While in your pharmacy, you notice multivitamins are on sale. After some thought, you decide that you may need a multivitamin. You would—
   A. Purchase the multivitamin and begin taking it regularly.
   B. Not take a multivitamin because it will cause a blood clot while taking DOACs.
   C. Start taking it and bring the multivitamin to your next Anticoagulants Clinic visit to show the pharmacist.
   D. Purchase the multivitamin but not start taking it until you talked with the pharmacist at your Anticoagulants Clinic. *

4. If you ran out of your prescription for your DOACs you would—
   A. Borrow DOACS from a friend, as long as it is the same dose as yours.
   B. Call and ask for refills for that day so you do not miss a dose of DOAC. *
   C. Do nothing because you have taken DOAC long enough, otherwise there would be more refills on your prescription.
   D. Wait until your next appointment that is just a few days away to get a new prescription.

5. Which of the following is an effect of DOACs medication that will most likely be experienced?
   A. Stroke.
   B. Leg Clot.
   C. Bruising.
   D. Blood in the urine. *
Appendices

6. You have a cold, which includes a runny nose and cough. You—
   A. Could safely take Day and Night Nurse (cold and flu medicine) to help get rid of the runny nose and cough.
   B. Take your friend’s medication that he/she uses for a bad cold because he/she is also on DOACs medication.
   C. Would call the Anticoagulants Clinic and tell him/her you are on DOACs medication and ask what you can take for your cold. *
   D. Decide it is safer to suffer through the cold because most cold medications will interact with your DOACs medication.

7. When making a dental appointment while taking DOACs medication, you need to remember you—
   A. Cannot have procedures done on your teeth while taking DOACs.
   B. Must tell your dentist you are taking DOACs well in advance of having any procedure done. *
   C. Can have procedures done and there is not a need to tell the dentist about the DOACs.
   D. Can have the dental procedure done if when you arrive at your dental appointment you tell the dentist you are taking DOACs.

8. When the need arises to take an antibiotic (to get rid of an infection) while taking DOACs you need to—
   A. Take half of the prescribed length of therapy, and then call the anticoagulants clinic.
   B. Refuse to take any new medication because you are taking DOACs.
   C. Wait until your next anticoagulants clinic visit and then tell the pharmacist about the antibiotic.
   D. Call the anticoagulants Clinic right away and let them know you are starting a new medication. *

9. The best time of day for me to take my DOACs is—
   A. At lunchtime.
   B. In the evening. *
   C. In the morning before breakfast.
   D. Any time of day when I remember.

10. Which of the following is an effect of my DOACs medication that I will most likely experience if my dose need to adjustment.
    A. A clot in the leg.
    B. Minor bleeding. *
    C. Clot in the lung.
    D. Bleeding in the brain.

11. Which of the following drinks can effect your DOACs work?
    A. Avonmore 2% low-fat milk.
    B. Mooju chocolate shake.
    C. Tropicana orange juice.
D. Ensure nutritional supplement. *

12. While taking DOACs, which of the following represents a situation when you should go to the emergency room?
   A. You cough up blood. *
   B. Your nose bleeds slightly while blowing it.
   C. Your gums bleed after brushing your teeth then it stops quickly.
   D. You have cut yourself while shaving and you control the bleeding.

13. Your neighbour brings over this great “all natural” herbal supplement she just bought from her chiropractor. She swears that this helps all her aches and pains and recommends that you take it when you ache. Your decision is to—
   A. Take her advice, realizing that you could use this herbal supplement.
   B. Start taking the herbal supplement and tell your pharmacist at the next office visit.
   C. Ask your pharmacist if the herbal supplement will interact with your medications before you take it. *
   D. Avoid taking herbal supplements altogether because all medications interact with DOACs.

14. While taking DOACs, you should call your Anticoagulants Clinic when you get:
   A. A backache.
   B. An upset stomach.
   C. A tension headache.
   D. Indigestion. *

15. While on DOACs you need to be routinely monitored for which of the following:
   A. PT/INR tests.
   B. Potassium levels.
   C. Blood glucose levels.
   D. Kidney function tests. *

16. Which of the following may have a significant effect on how well your DOACs work?
   A. Changes in your mood.
   B. Changes in sleep habits.
   C. How much water your drink.
   D. Using over the counter medications. *

17. While taking DOACs, which of the following should lead you to the emergency room?
   A. Loss of appetite.
   B. Brown loose stools.
   C. Urine becomes red in colour. *
   D. A quarter size bruise on your arm.

18. You have generic and brand DOACs tablets at home that are both the same dose. You should—
Appendices

A. Alternate days by taking brand on one day and generic on the next day.
B. Take only brand or generic, but not both. *
C. Not take either until you call the Anticoagulants Clinic.
D. Take both because they work differently.

19. After starting DOACs, how long (in months/years) would you expect to be taking DOACs?
   A. 1 year.
   B. 1 month.
   C. It depends on each person's needs. *
   D. If you start DOACs, you will have to be on the medication for the rest of your life.

20. Which of the following activities are more risky while taking DOACs?
   A. Playing football, because you can hit your head. *
   B. Taking a bath, because soap interacts with DOACs.
   C. Playing cards because using your hands a lot will cause a blood clot.
   D. Walking a lot, because exercise is not good for you while taking DOACs.
## Appendix 4

### Table A.1: CINAHL Plus (EBSCOhost) Search Strategy

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<td><strong>Result</strong></td>
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<td>S11 AND S18 AND S26</td>
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<td>S11 AND S16 AND S29</td>
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<td>S11 AND S18 AND S29</td>
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<td>S36</td>
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### Appendix 5

#### Table A.2: Cochrane Library Search Strategy

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<td>Betrixaban</td>
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<td>mobile or mobile health or m-health</td>
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<td>27962</td>
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<td>#45</td>
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<td>clinical outcome</td>
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<td>#13 and #21 and #43</td>
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<td>#13 and #25 and #43</td>
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<td>#52</td>
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Appendices
### Appendix 6

**Table A.3: ERIC Pro Quest Search Strategy**

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<td>0</td>
</tr>
<tr>
<td><strong>S2</strong></td>
<td>(warfarin OR coumadin OR coumarin* OR &quot;oral anticoagula**&quot;) AND (computer OR laptop) AND (edu* OR knowledge OR understand* OR &quot;drug information&quot; OR &quot;patient guid**&quot; OR counsel*).</td>
<td>0</td>
</tr>
<tr>
<td><strong>S3</strong></td>
<td>(warfarin OR coumadin OR coumarin* OR &quot;oral anticoagula**&quot;) AND (&quot;tablet or digital tablet&quot; OR iPod OR &quot;mp3 player&quot;) OR iPad) AND (edu* OR knowledge OR understand* OR &quot;drug information&quot; OR &quot;patient guid**&quot; OR counsel*).</td>
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</tr>
<tr>
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<td>(warfarin OR coumadin OR coumarin* OR &quot;oral anticoagula**&quot;) AND (internet OR application OR &quot;online or on-line&quot; OR software OR website OR &quot;electronic health or e-health&quot; OR &quot;virtual health&quot; OR technology OR intervention OR &quot;electronic program&quot;) AND (edu* OR knowledge OR understand* OR &quot;drug information&quot; OR &quot;patient guid**&quot; OR counsel*).</td>
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</tr>
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<td>(warfarin OR coumadin OR coumarin* OR &quot;oral anticoagula**&quot;) AND (&quot;smart phone or smartphone&quot; OR &quot;mobile or mobile health or m-health&quot; OR &quot;cell* phone&quot; OR iPhone) AND (&quot;adherence or</td>
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</tr>
<tr>
<td>Appendices</td>
<td>compliance or concordance&quot; OR &quot;INR or international normalised ratio or international normalized ratio&quot; OR &quot;clinical outcome&quot;).</td>
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</tr>
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<td>------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>S6</strong></td>
<td>(warfarin OR coumadin OR coumarin* OR &quot;oral anticoagula&quot;) AND (computer OR laptop) AND (&quot;adherence or compliance or concordance&quot; OR &quot;INR or international normalised ratio or international normalized ratio&quot; OR &quot;clinical outcome&quot;).</td>
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</tr>
<tr>
<td><strong>S7</strong></td>
<td>(warfarin OR coumadin OR coumarin* OR &quot;oral anticoagula&quot;) AND (&quot;tablet or digital tablet&quot; OR (iPod OR &quot;mp3 player&quot;) OR iPad) AND (&quot;adherence or compliance or concordance&quot; OR &quot;INR or international normalised ratio or international normalized ratio&quot; OR &quot;clinical outcome&quot;).</td>
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</tr>
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<td>(warfarin OR coumadin OR coumarin* OR &quot;oral anticoagula&quot;) AND (internet OR application OR &quot;online or on-line&quot; OR software OR website OR &quot;electronic health or e-health&quot; OR &quot;virtual health&quot; OR technology OR intervention OR &quot;electronic program&quot;) AND (&quot;adherence or compliance or concordance&quot; OR &quot;INR or international normalised ratio or international normalized ratio&quot; OR &quot;clinical outcome&quot;).</td>
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### Appendix 7

**Table A.4: Ovid (MedLine) Search Strategy**

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<td>betrixaban.mp.</td>
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<td>dabigatran etexilate.mp. or Dabigatran/</td>
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<td>AZD-0837.mp.</td>
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</tr>
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<td>#17</td>
<td>iPhone.mp. or Mobile Applications/</td>
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</tr>
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<td>14 or 15 or 16 or 17</td>
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# Appendices

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### Table A.5: PubMed Search Strategy

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7

#15
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294
| #16 | (((((((warfarin[Title/Abstract]) OR coumadin[Title/Abstract]) OR coumarin[Title/Abstract]) OR ((oral anticoagula*[Title/Abstract]) NOT (((((apixaban[Title/Abstract]) OR rivaroxaban[Title/Abstract]) OR betrixaban[Title/Abstract]) OR dabigatran etexilate[Title/Abstract]) OR AZD-0837[Title/Abstract])))) AND (((smart phone[Title/Abstract] OR smartphone[Title/Abstract]) OR (mobile[Title/Abstract] OR mobile health[Title/Abstract] OR m-health[Title/Abstract]) OR (cell phone[Title/Abstract] OR cellular phone[Title/Abstract]) OR iPhone[Title/Abstract])) AND (((adherence[Title/Abstract] OR concordance[Title/Abstract] OR compliance[Title/Abstract]) OR (INR[Title/Abstract] OR international normalised ratio[Title/Abstract] OR international normalized ratio[Title/Abstract]) OR clinical outcome[Title/Abstract]) | 34 |
| #17 | (((((((warfarin[Title/Abstract]) OR coumadin[Title/Abstract]) OR coumarin[Title/Abstract]) OR ((oral anticoagula*[Title/Abstract]) NOT (((((apixaban[Title/Abstract]) OR rivaroxaban[Title/Abstract]) OR betrixaban[Title/Abstract]) OR dabigatran etexilate[Title/Abstract]) OR AZD-0837[Title/Abstract])))) AND (((tablet[Title/Abstract] OR digital tablet[Title/Abstract]) OR iPod[Title/Abstract]) OR iPad[Title/Abstract])) AND (((adherence[Title/Abstract] OR concordance[Title/Abstract] OR compliance[Title/Abstract]) OR (INR[Title/Abstract] OR international normalised ratio[Title/Abstract] OR international normalized ratio[Title/Abstract]) OR clinical outcome[Title/Abstract]) | 85 |
| #18 | (((((((warfarin[Title/Abstract]) OR coumadin[Title/Abstract]) OR coumarin[Title/Abstract]) OR ((oral anticoagula*[Title/Abstract]) NOT (((((apixaban[Title/Abstract]) OR rivaroxaban[Title/Abstract]) OR betrixaban[Title/Abstract]) OR dabigatran etexilate[Title/Abstract]) OR AZD-0837[Title/Abstract])))) AND (((tablet[Title/Abstract] OR digital tablet[Title/Abstract]) OR iPod[Title/Abstract]) OR iPad[Title/Abstract])) AND (((adherence[Title/Abstract] OR concordance[Title/Abstract] OR compliance[Title/Abstract]) OR (INR[Title/Abstract] OR international normalised ratio[Title/Abstract] OR international normalized ratio[Title/Abstract]) OR clinical outcome[Title/Abstract]) | 11 |
| #19 | (((((((((warfarin[Title/Abstract]) OR coumadin[Title/Abstract]) OR coumarin[Title/Abstract])) OR ((oral anticoagula*[Title/Abstract]) NOT (((apixaban[Title/Abstract]) OR rivaroxaban[Title/Abstract]) OR betrixaban[Title/Abstract]) OR dabigatran etexilate[Title/Abstract]) OR AZD-0837[Title/Abstract]))) AND (((((((internet[Title/Abstract]) OR application[Title/Abstract]) OR (online[Title/Abstract] OR on-line[Title/Abstract])) OR software[Title/Abstract]) OR website[Title/Abstract]) OR (electronic health[Title/Abstract] OR e-health[Title/Abstract])) OR virtual health[Title/Abstract]) OR technology[Title/Abstract]) OR intervention[Title/Abstract]) OR electronic program[Title/Abstract])) AND (((adherence[Title/Abstract] OR concordance[Title/Abstract] OR compliance[Title/Abstract])) OR (INR[Title/Abstract] OR international normalised ratio[Title/Abstract] OR international normalized ratio[Title/Abstract])) OR clinical outcome[Title/Abstract]) | 569 |
Appendices
### Appendix 9

**Table A.6: Web of Science (Thomson Reuters) Search Strategy**

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