

**Development and evaluation of novel, personalisable
electronic counselling aids for patients starting Direct
Oral Anticoagulants (DOACs)**

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Declaration

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Abbreviations

AF	Atrial fibrillation
AKA	Anticoagulation knowledge assessment
AKT	Anticoagulant knowledge test
COVID-19	Coronavirus disease 2019
DCC	Directed cardioversion
DOACs	Direct oral anticoagulants
DVT	Deep vein thrombosis
ECG	Electrocardiogram
EHRA	European Heart Rhythm Association
ESC	European Society of Cardiology
FFP	Fresh frozen plasma
GOe	Global Observatory for eHealth
HCPs	Healthcare professionals
HPRA	Health Product Regulatory Authority
HSE	Health Service Executive
INR	International Normalised Ratio
iPACT	International Pharmacists for Anticoagulation Care Taskforce
IPU	Irish Pharmacy Union
JAKQ	Jessa atrial fibrillation knowledge questionnaire
JAKQ-VTE	Jessa atrial fibrillation questionnaire for venous thromboembolism
JREC	Joint research and ethics committee
KODOA	Knowledge of direct oral anticoagulants
MCQ	Multiple choice question
NALA	National Adult Literacy Agency
NLM	National Library of Medicine
NMIC	National Medicines Information Centre
NOACs	Novel oral anticoagulants
NTI	Narrow therapeutic index

NVAF	Non-valvular atrial fibrillation
OACs	Oral anticoagulants
OAK	Oral anticoagulant knowledge
PCC	Prothrombin complex concentrates
PDA	Personal digital assistant
PE	Pulmonary embolism
PEMAT	Patient education materials assessment tool
PVI	Pulmonary vein isolation
RCT	Randomised controlled trial
SE	Systemic embolism
SmPC	Summary of product characteristics
TTR	Time within therapeutic range
TUH	Tallaght University Hospital
VKAs	Vitamin K antagonists
VTE	Venous thromboembolism
WHO	World Health Organisation

Summary

Aims

To develop a novel education intervention in which patients are provided with customised information on their direct oral anticoagulant (DOAC) treatment in audio-visual format.

Methods

Two initial literature reviews, one of validated knowledge questionnaires for oral anticoagulant (OAC) patients, and one of electronic education for OAC patients, provided background and context for the research. An evaluation of the quality of counselling resources used to educate patients taking OAC was also conducted.

Subsequently, a knowledge questionnaire for DOAC patients was designed and an expert panel of healthcare professionals (HCP) validated the content. The questionnaire was piloted in a cohort of DOAC patients. A personalisable electronic counselling aid was created for future use in a randomised controlled trial.

Results

Six validated questionnaires were included in the knowledge questionnaire review, varying in OACs assessed, format, content, validation methods, and quality. There is a need for a standardised validation process to ensure consistent quality of questionnaires. Five studies were included in the electronic education review. While the studies showed mostly positive outcomes for their electronic education techniques, their small sample sizes limits the conclusions that can be made.

Findings from the evaluation of counselling resources show that patient resources were more likely to comply with the European Heart Rhythm Association (EHRA) guidelines than HCP resources. Manufacturer resources were more comprehensive for both patients and HCPs, and were more likely to comply with the EHRA and the international pharmacists anticoagulation care taskforce (iPACT) guidelines.

A knowledge questionnaire was produced for DOAC patients which requires a full-scale validation in the target populations. An electronic counselling aid was produced which may be personalised to the individual patient's characteristics

Conclusions

Further research is required in the area of validation of knowledge questionnaires for OAC patients to produce tools of a high standard. More adequately powered, good quality RCTs are needed in the area of electronic educational interventions. Counselling resources should be assessed for their quality prior to their use to ensure effective patient education. The knowledge questionnaire is prepared for validation in a large patient cohort. The electronic counselling aid can be used as an intervention in a RCT to evaluate its impact on patient knowledge and various other outcomes.

1. Introduction

This thesis is based on the development and validation of a knowledge questionnaire, and the design of an electronic counselling aid for use among patients in Ireland taking Direct Oral Anticoagulants (DOACs). Those who have worked on the evaluation of patients' anticoagulant knowledge previously include Briggs *et al.*, Zeolla *et al.*, Obamiro *et al.*, Desteghe *et al.*, Konieczynska *et al.*, and Metaxas *et al.* [1-6] All of these researchers have developed and validated forms of knowledge questionnaires for administration in patients taking oral anticoagulants (OACs). The subjects covered, quantity and format of questions, their intended use, and the anticoagulants these tools assess. The tools have not been validated in the same countries under the same conditions. A knowledge questionnaire for use in patients taking OACs for the prevention of stroke in atrial fibrillation or venous thromboembolism has not yet been developed and validated for the English language. Researchers who have worked in the area of electronic tools for the education of patients taking OACs include Clarkesmith *et al.*, Moore *et al.*, Talboom-Kamp *et al.*, Guo *et al.*, and Toscos *et al.* [7-11] Patient education is essential to ensure DOACs' safety and efficacy. Novel techniques to do so in a standardised and efficient, yet personalised manner must be explored. [12, 13]

1.1. ATRIAL FIBRILLATION

Atrial Fibrillation (AF) is one of the leading causes of stroke, heart failure, and cardiovascular morbidity in the world, despite the progress in the management of the arrhythmia. [14] The incidence of the condition is predicted to increase with time, as the aging population continues to rise. [15]

1.1.1. Signs and Symptoms

Signs and symptoms of AF can include palpitations, shortness of breath, exercise intolerance, chest pain and malaise. However, many patients, particularly the elderly, experience asymptomatic AF. [16]

1.1.2. Diagnosis and Treatment

An electrocardiogram (ECG) is commonly used to detect AF. Although a single ECG can be sufficient to diagnose the arrhythmia, often patients experience paroxysmal AF which would require a longer duration of monitoring to detect. In those experiencing daily AF symptoms, usually a 24- or 48-hour continuous Holter, a type of ambulatory electrocardiography device for cardiac monitoring, is

sufficient for diagnosis. Diagnosis in patients with nonspecific symptoms and long breaks between episodes can take years. [17]

The treatment of AF is based on: reducing symptoms, preventing thrombosis, and preventing cardiomyopathy. Stroke is the most common form of thrombosis associated with AF. [17] Created by Gregory Lip, MD, and colleagues, the CHADS₂DS₂-VASc score derived from the original CHADS₂ score, originally developed by Dr Brian Gage. [18, 19] Dr Lip developed the CHADS₂DS₂-VASc score to incorporate many common risk factors and modifiers not in the initial CHADS₂ score. The tool is used to assess the risk of thromboembolic events in patients with non-valvular atrial fibrillation (NVAf). [20] The risk of a patient suffering a stroke can be calculated using a CHADS₂DS₂-VASc score which can have implications for clinical management and treatment of patients. The tool uses a patient's age, sex, congestive heart failure, hypertension, stroke/thromboembolism/transient ischaemic attack, vascular disease, and diabetes history to calculate their stroke risk. Men with a score >1 or more, and women with a score >2 or more, should be considered to receive an anticoagulant to reduce this risk. [21] DOACs have emerged as the preferred drug choice over vitamin K antagonists (VKAs) for stroke prevention in AF, especially for patients newly initiated on anticoagulants. [14, 22, 23]

1.2. VENOUS THROMBOEMBOLISM

Venous thromboembolism (VTE) is an umbrella term used for the conditions of pulmonary embolism (PE) and deep vein thrombosis (DVT). VTE is a major global burden, occurring in approximately 1 in 1000 people annually and the incidence increases with age. [24, 25] VTE is responsible for the death of over 500,000 people in Europe each year. It is the third leading cause of cardiovascular deaths after myocardial infarction and stroke. [26] Roughly two-thirds of symptomatic cases of VTE are due to DVT and the remainder arise from PE with or without DVT. [25] A blood clot is produced as an outcome of the coagulation cascade. This cascade comprises a series of complex steps occurring in a specific sequence involving enzymes in the blood. It has a protective function, usually preventing blood loss following injury. However, the blood clotting system can also lead to thrombosis inside blood vessels. This is considered a VTE if the thrombosis occurs in the deep venous system. [27]

1.2.1. Deep Vein Thrombosis

DVT is when a blood clot or thrombus forms in the deep veins of the body, usually in the lower legs. [28] DVT can cause symptoms such as swelling, redness and leg pain. However, DVT can also be symptomless. [28]

1.2.2. Pulmonary Embolism

PE occurs when a DVT clot breaks away and lodges in the pulmonary circulation. Pulmonary vascular occlusion is when this clot causes a blockage and interrupts gas exchange and circulation. [29] PE may be asymptomatic or present as sudden death. However, the characteristic signs and symptoms associated with PE are non-specific and are present in many other conditions. Examples include tachycardia, dyspnoea, and chest pain. This explains why many PE episodes go undiagnosed and can be fatal. [29]

1.2.3. Diagnosis, Treatment and Prevention

Diagnosing VTE can include the application of a clinical decision rule and a D-dimer test. [30] This test looks for a small piece of protein, or D-dimer, which is produced when an enzyme plasmin cleaves fibrin to break down clots. Assays are used to confirm that the coagulation cascade is producing thrombin. [31] Venous compression ultrasonography is more commonly used as an initial diagnostic method as it is non-invasive and easy to administer. Other methods may be also used, such as magnetic resonance venography and venous phase computed axial tomography. [32]

Anticoagulants form the foundation of VTE treatment. The aim of treatment is to prevent thrombus extension or embolization, and to prevent new clots from forming. [25] DOACs are now more commonly recommended over VKAs for oral anticoagulation in VTE as they display similar efficacy with reduced bleeding risk and ease of use. [33] DOACs provide predictable dosing, more convenient perioperative management, no routine laboratory monitoring requirements, and have fewer food-drug interactions. [34]

Knowledge and understanding of the risk factors of VTE is essential to enhance the prevention of the disease in high risk patients. Major risk factors include: older age, obesity, cancer, hospitalisation, immobility, and oral contraceptives, to name a few. [24]

1.3. ANTICOAGULANTS

Anticoagulant medicines prevent or delay the blood from clotting. This is essential in circumstances where the blood clots too much, as blood clots can block blood vessels leading to conditions such as stroke or a heart attack. [35]

Oral anticoagulants are indicated to prevent and treat VTE and in the prevention of stroke and systemic embolism (SE) in adults with NVAF. [36, 37]

1.3.1. Warfarin

Warfarin, or coumadin, has been in use for over 60 years. It is a VKA and is derived from a naturally occurring plant, sweet clover (*Melilotus alba* and *M. officinalis*). [38] Warfarin became the mainstay of anticoagulant therapy due to its efficacy in preventing embolic strokes in patients with AF. [38] However, even with its longstanding use, warfarin is not without complications and its popularity has since declined among prescribers. [39] Patients taking warfarin are required to regularly monitor their international normalised ratio (INR) to ensure their coagulation levels are within target range. An INR test assesses the coagulation status of patients, using prothrombin time which measures the time it takes plasma to form a clot. [40] The dosage of warfarin is adjusted accordingly depending on the patients' INR. [41] Fluctuations in INR can occur for many reasons, such as a change in diet, poor compliance, consuming alcohol, seasonal variation (thought to be caused by individual seasonal changes in sensitivity to warfarin, in the consumption of vitamin K rich foods and/or alcohol, rates of febrile states due to infections, and variations in compliance), and interactions with other medicines. [42, 43]

Monitoring of a patient's blood levels can indicate their adherence to the medication, as fluctuations in INR can occur due to poor compliance. [42] Warfarin is a narrow therapeutic index (NTI) medicine, with many interactions. Drugs with NTIs have a narrow window between their effective doses and those at which they produce adverse side effects. [44] This makes it difficult for patients to remain in a defined anticoagulation range on warfarin. [38] Thankfully, there are multiple options available for warfarin reversal if needed such as vitamin K, prothrombin complex concentrates (PCC), or fresh frozen plasma (FFP) administration. [45]

1.3.2. Direct Oral Anticoagulants

Since 2008, new compounds with anticoagulant effects have been available on the European market for the licensed indication of thromboprophylaxis post orthopaedic surgery. [46] These substances are non-vitamin K antagonist oral anticoagulants and have been given a variety of different names. Referred to as novel oral anticoagulants (NOACs) and DOACs, they have a more targeted mechanism of action compared to warfarin. [47] There are currently four different DOACs on the market in Ireland: apixaban, rivaroxaban, edoxaban, and dabigatran, licensed for a variety of indications such as stroke prevention in NVAF and treatment of VTE. [48-52] The main advantages of DOACs is their lack of food and drug-drug interactions, predictable pharmacokinetics and pharmacodynamics, a rapid onset and offset of action, less requirement for routine laboratory monitoring, and reduced risk of intracranial haemorrhage. [47]

There are currently two licensed reversal agents for the DOACs in Ireland: idarucizumab and andexant alfa. Idarucizumab may be used to resolve severe uncontrolled bleeding associated with dabigatran intake. [53] Andexant alfa can be used to reduce the anticoagulant effects of apixaban and rivaroxaban in life-threatening or uncontrolled bleeding. Its use for edoxaban-reversal is not recommended due to lack of data. [54] Four-factor PCC has been analysed for its use in the reversal of DOACs, and preliminary study results are positive overall, but more data are needed. [55, 56] Four-factor PCC contains vitamin K-dependent coagulant factors and anticoagulant proteins which cause haemostasis. [57] It is not specific to DOACs, and was licensed for use in VKA reversal in Ireland in 2014. [58]

Due to their short half-life, adherence to DOACs is essential to ensure adequate stroke prevention and to reduce risk of VTE complications day-to-day in patients. If a dose is taken too soon compared to the intended regimen, patients are at an increased risk of bleeding-related complications. [59] DOACs were featured by the Irish State Claims Agency to be in the top twenty drugs involved in medication safety incidence in 2016. [60] Management of bleeding in individuals who are receiving a DOAC can be challenging as routine coagulation tests cannot generally be used to determine the level of anticoagulation, and some of the reversal agents are difficult to access and may be prothrombotic. [61] It is imperative that patients receive effective counselling regarding their condition and their treatment to improve DOACs' safety and efficacy.

1.3.3. DOACs versus Warfarin

Despite the numerous benefits of DOACs, warfarin remains an appropriate first-line treatment option for stroke prevention in NVAf in Ireland as per HSE guidelines (2019) when the patient's time in therapeutic range (TTR) is >70%. [46] Apixaban is the preferred DOAC for this same indication as the medication appears to have an advantage in terms of safety and reduced bleeding, compared to warfarin and other DOACs. [46] Prescribers may consider it for first-line treatment, particularly if there are tolerance issues and/or an unstable INR with warfarin. [46] As the HSE guidance is yet to be updated since 2019, warfarin is still the preferred choice of anticoagulant in stroke prevention in NVAf when possible due to its low cost. [52] Warfarin is still commonly used due to the long term experience of its use and its low cost. Newer therapies have not yet shown greater efficacy to warfarin with time in therapeutic range (TTR) >70%. [46] It is expected that the uptake of DOACs will only further increase as evidence shows reductions in major bleeding incidences compared to VKAs and their noninferiority with respect to overall efficacy in treatment. [62, 63]

The number of people receiving DOAC therapy has steadily increased in Ireland from 2013 to 2017. According to the primary care reimbursement scheme (PCRS) in December 2013 a total of 10,985 patients were dispensed a DOAC under the community drug schemes while 32,969 were dispensed warfarin. By December 2017, a total of 48,147 patients received a DOAC and 19,588 patients received warfarin. [52] This disparity is likely to have increased further in 2018 and 2019, and will likely continue in the future as the number of people in the elderly population rises. [64] Although the authors have requested more recent data from the PCRS regarding DOAC dispensing in Ireland, we have not yet received this data. The PCRS reported that expenditure on medicinal products classified under 'blood and blood-forming organs' in 2019 under the drugs payment scheme, a total of €17.39m was spent, with prescribing frequency of 647,237. [65]

Lack of routine monitoring with all DOACs can cause hesitation in prescribers, fearing that this could lead to reduced adherence. However, fear of non-adherence does not need to be a reason to avoid prescribing of DOACs, and prescribers should instead focus on patient education to improve any potential non-adherence. [66] In the management of chronic conditions, careful understanding of the individual patient's attitudes and behaviours is essential for a successful healthcare professional-patient communication. [67]

A wise approach to avoid medication adherence issues is to look at strategies learned from VKAs and other major medications commonly prescribed in the treatment of chronic disorders. One example from a study by Di Minno *et al.* to use follow up visits, and to employ open discussion and questionnaires regarding any motivational issues and priorities. This may prove crucial in the identification of barriers and individual direction to be pursued to ensure adherence. [67]

To ensure adequate care of the growing population of patients using DOACs, they must be appropriately educated about their DOACs. Warfarin has been studied thoroughly as regards effective methods of patient counselling. [42, 68-71] However, the same amount of research has not yet been conducted for DOACs. Two leading international bodies, the European Heart Rhythm Association (EHRA) and the International Pharmacists for Anticoagulation Care Taskforce (iPACT), have both produced recommendations for the counselling of patients DOACs. [13, 72] Further guidance from healthcare organisations would be beneficial for healthcare professionals educating these patients.

One of the primary advantages of warfarin is the ability to monitor its effects closely via the patients' INR values. A report published by the Health Service Executive (HSE) in 2012 stated that patients with controlled INR levels were tested every 6 weeks on average. [73] Uncontrolled INR

levels are associated with poor clinical outcomes such as increased rates of hospitalisation and likelihood of mortality. [42]

1.4. BASIS OF THE RESEARCH

Healthcare practitioners currently have limited time to give more essential information to patients due to being overstretched in the healthcare system. [74-76] Owing to this, patients are often provided with an avalanche of information when first diagnosed or prescribed a treatment. [77] Frequently, patients are trying to digest the diagnosis or the fact that they will have to take medication. They are less likely to understand the important health information being delivered to them in these moments due to overwhelm. [78]

It can be very difficult to communicate effectively and efficiently in these circumstances. Patients may be embarrassed or scared to ask questions or not know how to phrase the information they are finding challenging. [78] The direct link between patient education and improved outcomes is not yet proven, which highlights a gap in the research. However, patient education improves patient understanding and adherence to medical instructions. [79-81] It is therefore reasonable to suggest that by providing effective education, patients' health-related outcomes should improve. Education is most effective when tailored to each individual. [82] Knowledge questionnaires will help to discover what the patient may need assistance with and healthcare practitioners can discuss their answers together. [12] The Jessa Atrial Fibrillation Knowledge Questionnaire (JAKQ) is a 16-item questionnaire, developed by researchers in Jessa Hospital and Hasselt University in Hasselt, Belgium. It is intended to be completed by patients themselves, to assess their knowledge of anticoagulant therapy and atrial fibrillation. [4] The research of Desteghe et al. forms an important basis for our research. [4, 82-85]

DOACs are overtaking the place of warfarin for preferred anticoagulant in certain populations. [86] They are high risk medicines used to treat high risk conditions, so ensuring their safe and effective use is essential. [60]

1.5. IMPORTANCE OF THE RESEARCH

This subject is important due to the lack of research surrounding patient education.

Healthcare workers are consistently working under strict time constraints which do not allow for thorough patient counselling. [74] Patient education is emerging as an essential factor to improve patient outcomes. However, there is currently a lack of efficient techniques to provide for patient

education. [4, 12] Personalised education is far more efficacious for patients and means they will only be required to read information relevant to them. [82]

A tool to assess patients' knowledge could help to reveal areas of confusion to be addressed by healthcare practitioners. [87] Having patients watch an educational video would also benefit visual learners – those whose attention span for listening to speakers may be shorter than watching a video, for example. [88]

1.6. AIMS OF THE RESEARCH

This research project aimed to develop a validated questionnaire to assess patients' knowledge around their condition and treatment. A electronic counselling tool has also been created to provide personalised education to patients taking DOACs. Results of the questionnaire can be provided to healthcare practitioners and face to face counselling can then focus on areas of uncertainty or misunderstanding in the information. The intention is to improve patient knowledge, having secondary impact on patient-related outcomes such as adherence, hospitalisation etc. It is possible that the time taken for patient counselling may be reduced using these methods.

1.7. OBJECTIVES OF THE RESEARCH

- To trial and refine an English translation of the JAKQ for DOACs;
- To develop a variant of the JAKQ suitable for VTE patients using DOACs; and
- To create an electronic tool to provide personalised education to patients taking DOACs.

2. Knowledge Questionnaires for OAC Patients: A Literature Review

2.1. INTRODUCTION AND BACKGROUND

The purpose of this chapter is to discuss the existing literature surrounding questionnaires that assess patients' knowledge and understanding of oral anticoagulants. This research was carried out to discover previous influential work in the area and any conflicting work. It provides a background for the research conducted in this thesis and gives insight into its development, which begins at the formation of a knowledge questionnaire for patients taking DOACs.

The use of validated knowledge questionnaires to address specific knowledge gaps in patients taking DOACs has been recognised by the EHRA in their practical guide produced in 2018. [13] These knowledge questionnaires can be administered to the patient at the time of their visit, via online platforms, or self-administered by the recipient. The items in the questionnaires may have an MCQ-style format, closed, or open-ended questions. Their role is to assist healthcare professionals (HCPs) in providing effective education and revealing gaps within patients' knowledge. It is not intended to be a test for patients, rather a tool to highlight areas HCPs need to address.

Knowledge gaps concerning OACs have been reported frequently, in various populations. [7, 89-91] Such knowledge deficits are concerning due to the high risk nature of OACs. [60] Patients that receive education have demonstrated a significant increase in medication compliance across a range of chronic conditions in some studies. [81, 92]

Medication adherence is a worldwide issue in chronic illness. Up to 50% of patients are nonadherent to medications such as OACs. [93-95] It is defined by the World Health Organisation (WHO) as "the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider." [96] This explanation highlights the importance of shared decision making among patient and prescriber. A patient must be empowered to contribute in their consultation with their HCP so that a consensus is made on therapy and management of the condition. [12]

Patients with poor medication adherence may experience serious adverse events and consequences that affect their health, such as poor clinical outcomes, increased hospitalisations, lower quality of life, and higher overall health costs. [92] Patient education has been shown to improve medication adherence across various conditions and disease states. [97]

2. Knowledge Questionnaires Literature Review

Poor health literacy levels are associated with poor warfarin and AF knowledge. [98, 99] Additionally, studies have shown that poor warfarin knowledge and lack of education about warfarin is associated with inadequate anticoagulant control and increased haemorrhagic events. [90, 98, 100] Patients with the highest risk of stroke were seen to have the poorest knowledge levels regarding their treatments. [90, 98, 100] Similar studies with patients taking DOACs have yet to be conducted.

Although DOACs are easier to manage than warfarin, with fewer interactions and monitoring required, medication adherence still remains vital for effective outcomes. Due to their short half-lives, irregular or missed doses of DOACs increase the risk of stroke, as patients will be inadequately anticoagulated during this time. [101, 102]

The European Society of Cardiology (ESC) has recommended an integrated approach to decision making so that patients are involved with their treatment choice. [14] Patient satisfaction with treatment has also been linked to compliance. [97] Patients should be equipped and empowered through education to promote self-management. Both the EHRA and the ESC have acknowledged that more research is needed to determine the best method to provide education for DOACs. [13, 14] An educational effort should be made to increase patient knowledge and clarify any misconceptions about the condition. [97]

2.1.1. Importance of the Review

Prior to developing a knowledge questionnaire and conducting a research study to validate it in the Irish population, a background knowledge of the current literature is required. Findings from similar research could be extremely useful in providing insight into our study. This review will provide readers with a detailed understanding of the processes involved in the development and validation of a knowledge questionnaire, and what has been conducted thus far in the research.

2.1.2. Aims and Objectives

1. To discover current validated knowledge tools for those taking oral anticoagulants with AF or VTE;
2. To compare and contrast these tools; and
3. To analyse which tools have been adapted and studied in other populations under alternative circumstances.

2.2. METHOD

2.2.1. Search Strategy

Electronic search of the databases was conducted using PubMed NLM (National Library of Medicine), EMBASE, and the Cochrane library to identify potentially relevant literature. A search strategy was developed to find studies involving the use of knowledge questionnaires to educate orally anticoagulated patients. Study titles and abstracts were initially screened to filter out relevant materials. The search was conducted between May and November 2020. Boolean operators (AND, OR) were utilised in the search strategy to effectively combine concepts. The search results were limited to English-language only.

The literature search strategy is outlined below.

Table 2-1: PubMed (MEDLINE) Literature search strategy

PubMed (MEDLINE) Literature Search Strategy		
#1	("knowledge"[Title/Abstract] OR "understanding"[Title/Abstract] OR "comprehension"[Title/Abstract] OR "education"[Title/Abstract])	1,938,418
#2	("questionnaire*" [Title/Abstract] OR "survey*" [Title/Abstract] OR "test"[Title/Abstract] OR "form"[Title/Abstract]) OR ("device"[Title/Abstract] OR "tool"[Title/Abstract] OR "instrument"[Title/Abstract] OR "mechanism"[Title/Abstract])	5,100,210
#3	("doac*" [Title/Abstract] OR "noac*" [Title/Abstract] OR "direct oral anticoagula*" [Title/Abstract] OR "novel oral anticoagula*" [Title/Abstract] OR "anticoagula*" [Title/Abstract] OR "dabigatran" [Title/Abstract] OR "apixaban" [Title/Abstract] OR "rivaroxaban" [Title/Abstract] OR "edoxaban" [Title/Abstract])	104,261
#4	("patient"[Title/Abstract] OR "counselling"[Title/Abstract] OR "counseling"[Title/Abstract] OR "counsel"[Title/Abstract])	2,492,778
#5	#1 AND #2 AND #3 AND #4 [Limits: English language]	2,530

Table 2-2: EMBASE Literature Search Strategy

EMBASE Literature Search Strategy		
#1	knowledge:ab,ti OR comprehension:ab,ti OR education:ab,ti	1,455,275
#2	questionnaire:ab,ti OR survey:ab,ti OR devices:ab,ti OR tool:ab,ti OR test:ab,ti	3,992,188
#3	doac:ab,ti OR noac:ab,ti OR 'direct oral anticoagulant':ab,ti OR 'novel oral anticoagulant':ab,ti OR 'anticoagulant agent':ab,ti OR apixaban:ab,ti OR edoxaban:ab,ti OR dabigatran:ab,ti OR rivaroxaban:ab,ti	22,005
#4	patient:ab,ti OR counseling:ab,ti	3,696,402
#5	#1 AND #2 AND #3 AND #4 [Limits: English language]	147

Table 2-3: Cochrane Literature Search Strategy

Cochrane Literature Search Strategy		
#1	(test):ti,ab,kw OR (questionnaire):ti,ab,kw OR (survey):ti,ab,kw OR (form):ti,ab,kw	530,600
#2	(device):ti,ab,kw OR (tool):ti,ab,kw OR (instrument):ti,ab,kw OR (mechanism):ti,ab,kw	194,018
#3	(DOAC):ti,ab,kw OR (NOAC):ti,ab,kw OR (direct oral anticoagulant):ti,ab,kw OR (novel oral anticoagulant):ti,ab,kw OR ("oral anticoagulant"):ti,ab,kw	2,959
#4	(apixaban):ti,ab,kw OR (dabigatran):ti,ab,kw OR (edoxaban):ti,ab,kw OR (rivaroxaban):ti,ab,kw	3,357
#5	#3 OR #4	5,301
#6	(patient):ti,ab,kw OR ("counseling"):ti,ab,kw	982,436
#7	#1 AND #2 AND #5 AND #6	44

2.3. RESULTS

2.3.1. Overview

A total of 2757 papers were identified through searching the databases. An additional 13 papers were identified through other sources, such as searching a relevant paper's reference list. After duplicates were removed, a total of 2727 papers remained. Through screening of titles and abstracts, 2679 were excluded from the review. Full-text articles were retrieved for 48 papers, where 38 papers were excluded due to having an incorrect intervention, the paper having been an abstract for a conference, or no full-text being available. A total of 10 studies were included for qualitative synthesis. A PRISMA flow diagram includes detailed information about the total number of studies identified, de-duplication, and numbers included and excluded. See Figure 2.1.

2. Knowledge Questionnaires Literature Review

A total of six papers were found to detail the development and validation of knowledge tools for administration to patients taking OACs: Briggs *et al.*, [1] Zeolla *et al.*, [2] Metaxas *et al.*, [6] Desteghe *et al.*, [4] Obamiro *et al.*, [3] and Konieczynska *et al.*. [5] The tools were titled as follows: the Anticoagulation Knowledge Assessment (AKA), the Oral Anticoagulant Knowledge (OAK) Test, the Knowledge of Direct Oral Anticoagulants (KODOA) Test, the JAKQ, the Anticoagulant Knowledge Test (AKT), and the JAKQ for VTE (JAKQ-VTE). [1-6] These tools will be discussed and reviewed in depth throughout this review.

A number of studies made use of previously validated knowledge questionnaires and administered them amongst different populations. [7, 84, 85, 103-109] Studies conducted by Smith *et al.* and Lane *et al.* seemed to develop knowledge tools that were used to assess participants' knowledge before and after an educational intervention. [90, 110]

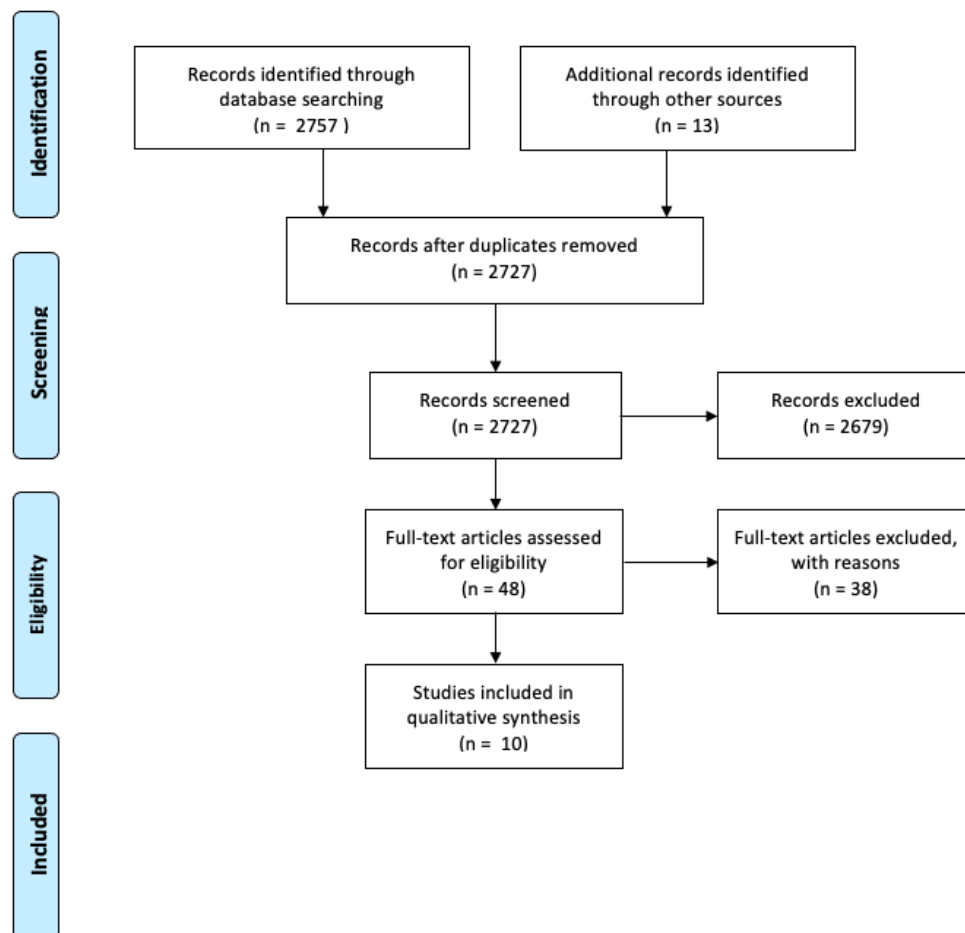


Figure 2.1: PRISMA Study Flow Diagram

2.3.2. Anticoagulants Assessed in Validated Questionnaires

The AKA, OAK, AKT, JAKQ, and JAKQ-VTE all include options for patients taking warfarin. The KODOA-test is the only tool that does not cater for these patients. Conversely, the AKA and OAK tests do not assess DOAC patients. Table 2-4 shows the differences between each questionnaire. Only three of the tools assess both warfarin and DOACs. [1-6]

Table 2-4: Anticoagulants Assessed in Validated Questionnaires

	Warfarin	DOACs	Year of Development
AKA [1]	✓		2005
OAK [2]	✓		2006
AKT [3]	✓	✓	2016
JAKQ [4]	✓	✓	2016
JAKQ-VTE [5]	✓	✓	2018
KODOA-test [6]		✓	2018

2.3.3. Intended Use

Each of the knowledge questionnaires are intended to be used to discover patients' knowledge of their medical condition (AF or VTE) and their medicines, whether they are taking DOACs or warfarin. The AKA is intended to be delivered to patients by clinical pharmacists. [1] The OAK, AKT, JAKQ, JAKQ-VTE and KODOA-test can all be self-administered by patients and therefore could be used widely in other healthcare settings. [2-4, 6, 111]

2.3.4. Format of Validated Questionnaires

The AKA includes 29 questions. [1] They are in a multiple choice question (MCQ) format with four potential options with one correct answer. Participants in the validation study completed the tool within 20 minutes. The AKA validation took place in two clinical sites in Chicago, Illinois, USA and the tool was developed in the English language. [1]

The OAK consists of 23 questions, also in the form of MCQs with one correct answer out of a possible four. [2] The authors do not disclose how long it took participants to complete the questionnaire, but with fewer items than the AKA it is likely to be less than 20 minutes in total. Zeolla *et al.* conducted the validation in the North-eastern US. [2] Although not specified, it is presumed the questionnaire was validated in the English language, due to the study location.

The AKT differs to the previous tools in that it entails 28 questions in an open-ended style and MCQ mix. The use of this style of question was due to authors' concerns that the MCQ format artificially raised a participant's knowledge score as it enables guessing and provides a clue with the correct

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answer. Completion of the AKT took participants between 15 to 20 minutes in the validation study. The tools' validation was completed in Tasmania, Australia. [3] Owing to this, one can assume that the AKT was developed in the English language.

The JAKQ is a 16-item questionnaire – 8 of which are specific to oral anticoagulants and the rest referring to atrial fibrillation. [4] The questions are MCQ style including one correct answer, two distractors and one “I do not know” option to discourage participants from guessing the answer. This is hoped to lead to a more accurate knowledge score. Participants took 6.5 minutes on average to complete the questionnaire during validation. The questionnaire was developed by researchers in Jessa Hospital and Hasselt University in Hasselt, Belgium. The JAKQ is a Dutch language questionnaire. [4]

The JAKQ-VTE was developed based on JAKQ for patients with VTE taking oral anticoagulants. [5] It contains the same number and style of questions, but 8 of which relate to VTE rather than AF. The authors reported that participants took between 3 to 15 minutes to complete the tool, 7 minutes on average. JAKQ-VTE therefore took participants slightly longer than JAKQ, despite the questions being closely aligned in number, format, and content to the JAKQ. But the JAKQ-VTE is still a relatively quick knowledge tool. The JAKQ-VTE is a Polish language questionnaire. [5]

Finally, the KODOA-test contains 15 MCQ style questions; each having one correct answer and two incorrect ones. [6] Participants in the study completed this test within 8 minutes in total. The participants were recruited in Basel City and Munchenstein, Switzerland and the German version was validated. [6]

All questionnaires used an MCQ style for the format of questions included, which is considered the most appropriate and efficient method for assessing cognitive function. [112] Each tool was delivered in written format, allowing for self-administration by patients.

2.3.5. Content

There are many similarities in the topics of education covered in the questions in each of the tools. However there are also some differences.

The AKA is based on ten content areas which were decided upon following a review of the published literature and protocols used in anticoagulation clinics. Anticoagulation pharmacists working in the clinics were interviewed by the researchers on the areas they felt were most important when educating a patient on anticoagulants. The content areas included were: medication, medication

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administration, medication interactions, activity, diet, side effects, pregnancy, informing health care providers, procedures, and laboratory monitoring. [1]

Subjects for the OAK were nominated by an expert panel consisting of two pharmacists, one nurse and one physician. They selected five areas of particular weight when developing a knowledge tool: basic drug information, adverse effects, drug-drug interactions, dietary issues, and monitoring. [2]

The AKT was developed after a review of the available literature around patient knowledge of anticoagulation. Five essential knowledge domains were identified, similar to the OAK: basic drug information, adverse drug effects, drug-drug interactions, drug monitoring, and dietary issues. [3]

The JAKQ aimed to assess patient knowledge of not only anticoagulation but also of AF. This was a new approach in comparison to the tools previously discussed which focused on assessing patients' knowledge of anticoagulation alone. The JAKQ was developed based on information from four sources: other questionnaires, an education checklist for healthcare professionals, education topics for AF patients on oral anticoagulation therapy, and information on support websites for AF patients. The tool's content was validated by a panel of healthcare professionals (doctors, pharmacists and nurses) with experience and expertise in the area. [4]

The JAKQ-VTE mirrors the format of the JAKQ in terms of content. The choice of additional questions regarding VTE were discussed by investigators to reach a consensus. The healthcare professionals represented in the group of investigators was not disclosed in the research study. Questions related to drug treatment cover: administration, missed doses, adverse effects, drug-drug interactions, operations or procedures, and monitoring. [111]

Finally, the KODOA-test was developed from information found following a review of the literature as well as drug summaries of product characteristics (SmPCs) and practice guidelines on DOACs. A total of nine topics formed the tool's basis: underlying disease, risk-benefit of treatment, mode of action, application and treatment adherence, accessing healthcare providers, relevant blood tests, medication interactions, diet and lifestyle, and self-care. During the content validation phase, topics such as diet and lifestyle were discarded from the questionnaire. To ensure content validity, the questionnaire was reviewed by 10 anticoagulation experts: 8 pharmacists and two physicians. These HCPs rated each question for its relevance. [6]

Overall, the subjects covered in each questionnaire are very similar. For example, all tools include basic drug information, drug-drug interactions, and laboratory monitoring. Most authors approached the decision with an initial review of the current literature and protocols used in

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practice for OAC counselling. [1, 3-5] Some research teams also used a panel of healthcare professionals with experience in the area to come to an agreement on content of the questionnaires. [1, 2, 4] Desteghe *et al.* looked at questionnaires previously developed to aid their content creation. [4] To broaden the scope of a tool, it could be beneficial to collaborate with HCPs and patients across different settings (primary, secondary and tertiary) and in different countries during development. Critical analysis of each subject under consideration is necessary to avoid overlap and create a concise, effective tool.

All studies included patients taking the relevant OACs in the study, which adds to the relevance of each tool. Obamiro *et al.* included subgroups of the general public and pharmacists as well to compare results. [3]

2.3.6. Validation Methods

The AKA was reviewed for content, readability and form by two independent reviewers who had expertise in item writing. [1] Construct validity was conducted using the Rasch dichotomous model. This analysis method identifies questions likely to be misunderstood by patients and areas where patients may be guessing. [113] It is also useful in its sample size where only 30 patients are required to obtain sufficient estimates.

The pilot study for the AKA was conducted at two pharmacy-managed antithrombosis clinics. 60 patients were recruited in total. Marzano's Taxonomy was used for questionnaire content validation. Three questions were deleted from the original 31-item questionnaire based on the results from the Rasch model used for construct validation. This then left a 29-item questionnaire including questions of varying difficulty.

Content validation was conducted for the OAK by an expert panel who also created the instrument. Each question was ranked on its level of importance by the panel. A pilot study with 11 participants on warfarin therapy led to the rewording of some items based on participant feedback. Face validation was completed with 102 participants – 75 of which were on warfarin and 27 were not. Retesting was done with 32 participants less than three months after initial testing. Following this, 3 questions were removed, resulting in a final 20-item tool. Construct validity was confirmed by significantly higher knowledge scores in participants taking warfarin than those not taking warfarin. The test-retest method confirmed the reliability of the questionnaire. Subjects were recruited from two suburban chain community pharmacies, two suburban supermarket pharmacies, one urban anticoagulation clinic, and an urban family medicine practice. [2]

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The AKT's content was validated by ten anticoagulation experts consisting of eight pharmacists and two physicians. Each item was graded for relevance by the panel on a scale of 1-4. This led to the separation of the instrument into part A (general anticoagulation questions) and part B (warfarin specific questions). Three groups of subjects conducted construct validation; 44 pharmacists recruited from community and hospital pharmacies, 50 patients on anticoagulants recruited from community pharmacies, and 50 people not taking anticoagulants recruited from public places (e.g. parks, bus stops, and shopping malls). Those taking anticoagulants scored significantly higher than those not, confirming construct validity of the tool. Test-retestability and internal consistency were also shown. [3]

Validation of the JAKQ involved both outpatients and hospital inpatients. The process included content validation, face validation, response process, construct validity, and reliability and sensitivity testing. A panel of experts composed of 5 electrophysiologists, 10 general practitioners, and 12 nurses carried out content validation. JAKQ was presented to 466 patients with AF, from both outpatients at the cardiology clinic and patients on the cardiology wards. Face validation was undertaken by 78 AF patients randomly selected to participate. Response validation was confirmed using a "think aloud" method in 20 AF patients. The test-retest method confirmed the tool's reliability. [4]

The JAKQ-VTE research paper lacked detail regarding the validation process and focused on the statistical nature of the responses. [5] This is perhaps due to the fact that the JAKQ-VTE is largely based off of JAKQ, which has already gone through a rigorous validation process (as outlined above) to test the knowledge of AF patients. A total of 273 VTE patients took the JAKQ-VTE as part of its validation process. Participants recruited had documented VTE and were referred for further diagnostic work-up to the John Paul II Hospital in Krakow. The completed questionnaires were collected by doctors who gathered general information about patients and medical data. A total score was calculated from finalised questionnaires and presented as a percentage. The finalised version of JAKQ-VTE was tested for sensitivity in 27 VTE patients, who received education based on incorrect answers and resat the questionnaire after 3-4 months. [5]

Content validation of the KODOA-test was conducted by an expert panel of four nurses, four pharmacists, and four physicians, all of whom had a history of treating DOAC patients. [6] Construct validation was carried out with a group of 32 patients and 28 pharmacists. Participants were recruited in three dedicated community pharmacies, where pharmacy staff asked patients with a DOAC prescription to participate. Reliability and internal consistency was confirmed by the results of each patient participant repeating the test approximately two weeks after the initial test. [6]

2. Knowledge Questionnaires Literature Review

Initial pilot testing among intended users is an important part of the validation process for questionnaires. The questionnaire should be administered to a relatively large sample size of respondents, or else the sampling errors may reduce statistical power of the validation. [114] The JAKQ was piloted in the largest sample size of 466 patients, providing greater statistical power in the results produced. [4] The consistency of a questionnaire can be determined using test-retest reliability and internal consistency. [114] Four of the tools, the OAK, AKT, JAKQ and KODOA test, conducted reliability testing. [2-4, 6] The validity of a questionnaire is assessed by analysing whether it measures what it intends to. Content and construct validity are the two major types of validation that should be done on a questionnaire. [114] All questionnaires underwent both content and construct validation, however the details were unclear in the research paper for the JAKQ-VTE.

2.3.7. Quality of Validation Studies

The quality of each study was considered using the AGREE II reporting checklist. [115] This method covers six domains, with an overall assessment at the end:

- Scope and purpose
- Stakeholder involvement
- Rigour of development
- Clarity of presentation
- Applicability
- Editorial independence

2.3.7.1. Scope and Purpose

The overall objective(s) of each study is clearly defined in the beginning of each document. The population to whom the study relates to is specifically described. The objective of the studies is similar: to develop and validate a questionnaire to test the knowledge of patients. The type of patient varies slightly depending on the study: patients taking warfarin anticoagulants (Briggs *et al.* and Zeolla *et al.*), patients taking OACs (Obamiro *et al.*), patients with AF (Desteghe *et al.*), patients taking DOACs (Metaxas *et al.*), and patients with VTE taking OACs (Konicynska *et al.*). [1-6]

2.3.7.2. Stakeholder Involvement

This domain ensures that the authors have sought the views and preferences of the target population when developing the piece. Briggs *et al.* involved anticoagulation pharmacists to gain insight into their practices and to develop the content areas included in the questionnaire. The AKA

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instrument was pilot tested in warfarin patients receiving anticoagulation education and counselling. [1] The OAK test was validated for its content by four nationally recognised experts in the area of anticoagulation therapy, included 2 pharmacists, a nurse, and a physician. Adults receiving warfarin therapy were recruited to participate in the study from community pharmacies, supermarket pharmacies and an anticoagulation clinic. [2] The AKT was presented to anticoagulation experts (8 pharmacists and 2 physicians), and a pilot study was conducted in 5 pharmacists, 3 patients, and 5 members of the general public. The test was validated in a larger cohort of pharmacists, OAC patients and the general public. [3] Desteghe *et al.* involved an expert panel of electrophysiologists, general practitioners and nurses with experience in the management of AF patients, as well as AF patients in the validation of the JAKQ. [4] Metaxas *et al.* involved a panel of experts (4 nurses, 4 pharmacists, and 4 physicians) with experience with DOAC patients to validated the content of their questionnaire. DOAC patients were also recruited for the validation study. [6] Finally, the JAKQ-VTE recruited patients with VTE being treated with anticoagulants for at least a month to complete their questionnaire. However, no healthcare professionals were listed as being involved in the tool's development. [5]

2.3.7.3. Rigour of Development

This domain entails the methods used as well as the strengths and limitations, benefits, side effects and risks of the study. Briggs *et al.* used the Rasch dichotomous model to evaluate the responses provided by the AKA tool. The authors fail to mention any limitations associated with the study. [1] Validation of the OAK test was detailed in the paper, involving content validation, construct validation, and test-retestability. The statistical analyses were defined in depth. Limitations of the study were: a lack of diversity in the patient population, a relatively small sample size for generalisation of results, the reading level of the instrument may exclude patients with limited education, patients not receiving warfarin had a higher average score than expected of the test (52%), the MCQ format permitted guessing, and participants who are cognitively impaired were not specifically excluded. [2]

Obamiro *et al.* outlined their validation process fully, including the statistical analyses methods used. The study limitations are as follows: the participants recruited in the general public group had high levels of education, the participants across the three groups were not age matched, participants were given the option of completing the questionnaire in person or via post, therefore it is impossible to know if participants that chose the latter accessed any resources to aid their answers. The high scores of the patient group could have been due to recruitment of highly motivated and enthusiastic patients, and may not reflect the broader population, and not all

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patients completed a second test for test-retest reliability. Furthermore, the study was conducted in a single region, and therefore limits the generalisability of the results. [3]

The validation process of the JAKQ was outlined clearly by Desteghe *et al.*, as well as the statistical analyses. The study limitations were as follows: the data collected was in one large tertiary care centre, therefore generalisability of the results to other settings should be done with caution, the JAKQ score will depend on the education provided in the hospital, and the study did not take cognitive problems into account which may have influenced the score of the JAKQ. [4]

Validation and statistical methods for the KODOA test were thoroughly defined by Metaxas *et al.*. The limitations acknowledged were that 52.3% of patients refused to participate in the study, the small number of participants limits the generalisability of results, only patients taking rivaroxaban and apixaban were included, missing out on dabigatran and edoxaban patients, and the MCQ format permits guessing. [6]

Lastly, study methods and statistical analyses were outlined by Konieczynska *et al.*. The validation process was not as in-depth as previous studies, and it involved the recruitment of participants to complete the questionnaire. Sensitivity testing of the final JAKQ-VTE was carried out in a small group of patients, receiving education on the incorrectly answered questions. No study limitations were provided. [5]

2.3.7.4. Clarity of Presentation

All studies' findings and conclusions were presented clearly, and the key recommendations for future use of each tool was communicated. [1-6]

2.3.7.5. Applicability

The future recommendations and limitations presented for each study allow the applicability of the questionnaires to be easily understood. The intended use of each tool is also clear in each study. [1-6]

2.3.7.6. Editorial Independence

Funding measures were listed for Zeolla *et al.*, Desteghe *et al.*, Obamiro *et al.*, and Metaxas *et al.*. [2-4, 6] Potential conflicts of interest were addressed, even if none existed, by Desteghe *et al.*, Konieczynska *et al.*, and Metaxas *et al.*. [4-6] Briggs *et al.* did not address any funding or conflicts in their research paper. [1]

2.3.8. Validated Questionnaires Used in New Settings

2.3.8.1. AKT

The original AKT was validated in three groups: pharmacists from hospital pharmacies, patients taking oral anticoagulants in community pharmacies, and the general public. The tool was validated in the English language. [3] The AKT was translated from English to Italian to cater to the Italian population and the I-AKT was created through the Brislin's translation model for cross-cultural research. [103]

This process involves conducting a translation, back-translation and forward translation. [116] Quantitative and qualitative content validity was performed for the I-AKT with a group of 14 anticoagulation experts to rate the pertinence and relevance of each item in the questionnaire, and to assess the clarity and comprehensibility of the questions. The same number of questions were retained for the I-AKT as in the original AKT – 28 items in total, with a mix of open-ended and MCQ style. The construct validity was performed by recruiting healthcare providers with experience in OAC patient management (n=124), patients receiving OAC treatment (n=113), and the general public (n=97). Patients were recruited in two anticoagulation clinics and had been receiving treatment for at least three months beforehand. The results of the study showed that healthcare providers had higher knowledge levels than patients taking OACs, and patients' knowledge was higher than that of the general public participants. This suggests that the I-AKT can discriminate between varying knowledge levels. This research further supports the validity and reliability of the AKT and the mono-dimensionality of the items in the tool. The AKT could be useful in a non-English setting for knowledge assessment of patients and in developing patient education materials. [103]

2.3.8.2. OAK Test

The OAK test was adapted from its original English language into Brazilian Portuguese due to a lack of validated instruments to assess patient knowledge about warfarin therapy. The psychometric properties of the OAK test were assessed during this study conducted by Praxedes *et al.* The Brazilian version of the OAK test consisted of 20-items in an MCQ-style, containing four possible answers with only one correct option. [104] The study was carried out in an anticoagulation clinic of a university hospital in south-eastern Brazil. Recruited patients (n=201) had a history of warfarin treatment for at least two months prior to the trial. [117] The instrument showed good psychometric properties. It was also assessed for internal consistency and reproducibility in the same study. A strong positive correlation was revealed between time within therapeutic range (TTR) values and the values of the level of knowledge assessed by the OAK test. [104]

2.3.8.3. JAKQ

A research study was conducted to evaluate the regional differences among Polish patients in their knowledge of AF diagnosis and OAC use. [105] The Polish translation of JAKQ was used in this study as the method of assessing patient knowledge. Patients with documented AF were recruited (n=1525) in the John Paul II Hospital in Krakow, which is a tertiary care centre; in a cardiology ward in the District Hospital in Torun and in a cardiology centre in Kielce. The final group of recruited patients were a mix of inpatient and outpatients. Patients were taking anticoagulants for 18 months (5-48 months) on average. The research showed that significant differences in patients' knowledge exists amongst various regions in Poland. NOAC patients scored worse than those taking warfarin. [105]

The research team that produced the JAKQ ran a study assessing the effect of individualised education sessions on patients' knowledge levels. The questionnaire was completed upon multiple hospital visits by each participant to test their knowledge levels. Any knowledge gaps revealed by the JAKQ were used during the individualised educational sessions. Patients receiving these sessions scored significantly better on JAKQ over time, confirming sensitivity of the JAKQ. [82] Similarly, a study was conducted by Desteghe *et al.* to evaluate the effect of an online tailored education platform to inform AF patients undergoing a direct cardioversion (DCC) or a pulmonary vein isolation (PVI). The JAKQ, with additional procedure-specific questions, was completed by participants at various timepoints before, during and after their procedure. Those receiving the online education had significantly improved knowledge at hospitalisation vs. baseline, which was retained post-procedure. [84]

2.3.9. Documented Questionnaires With No Specific Validation

2.3.9.1. Smith *et al.*

A study conducted by Smith *et al.* researched AF patients' warfarin knowledge using a 52-item questionnaire. [90] Researchers wanted to see the impact of warfarin knowledge on their risk of adverse events and the implication for safety, efficacy, and education strategies. Patients were recruited from a clinical practice in Utah, USA, so it is presumed the questionnaire was developed in English. A total of 100 patients were surveyed for the study. The questionnaire used in the study was reviewed by two dietitians and a cardiologist for content validity, contained 52-items, with a mix of MCQ-style and open-ended format. The questionnaire was self-administered by patients. However, the questionnaire was not pilot tested and was made based on warfarin education practices at the time. Subjects covered in the questionnaire included general warfarin knowledge, compliance, drug interactions, herbal or vitamin interactions, and diet. Participants were divided

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into groups based on their duration of warfarin use, which ranged from less than 1 year to more than 5 years. The results showed that those at highest risk of stroke had very low knowledge scores. Specific areas with low knowledge levels in the population were drug interactions, herbal or vitamin interactions, and diet. The average scores for each topic in the questionnaire was 17%, 7%, and 23% respectively. [90]

2.3.9.2. *Lane et al.*

Lane *et al.* conducted a study around patient knowledge of AF and anticoagulant therapy, and the effects of an educational intervention programme. The team developed a standardised questionnaire in English to appraise patients' knowledge of AF and the potential benefits/side effects of their anticoagulant therapy. It contained a total of 14 items and each question was closed-ended, such as "Do you know what atrial fibrillation is?". This questionnaire was given at baseline and follow up appointments in the outpatient clinic. Researchers provided an information booklet and education to patients during their visit. Results of the baseline questionnaire showed a lack of knowledge in patients which could be somewhat improved following education with an information booklet. [110]

An overall summary for each of the questionnaires listed is available in Summary Tables of Knowledge Questionnaires.

2.4. DISCUSSION

Knowledge questionnaires have the potential to be a useful technique of identifying knowledge deficits and to target education specifically to the needs of each individual patient. [22] Several studies have shown the value of questionnaires to reveal patients' knowledge gaps, allowing educational interventions to be tailored to the individual. [82, 85] For example, a randomised controlled trial conducted by Desteghe *et al.* showed that the JAKQ is an effective and feasible tool to provide targeted education to AF patients. Patients' knowledge levels improved significantly after one educational session based on the completion of the JAKQ. [82]

2.4.1. Anticoagulants Assessed

As DOACs gain popularity amongst prescribers, it would be reasonable to expect that tools developed in the future will focus more on these drugs rather than warfarin. [86] However, due to the longstanding history of warfarin use as an anticoagulant, it is not surprising that 5 out of 6 validated knowledge tools assess warfarin knowledge. [1-5] By including options for both warfarin and DOAC patients, researchers can guarantee a broader uptake of the tool whilst also allowing healthcare professionals to only become accustomed to one tool. It also facilitates comparison of knowledge levels of patients taking VKAs and DOACs.

2.4.2. Intended Use

As expected, all tools are intended for use in a similar area – to assess patients' knowledge at the beginning of their treatment and continuously to monitor progress. This would permit determination of the link between patient knowledge and outcomes. They are also useful for healthcare providers to tailor their education to each patient specific to their knowledge deficits. A validated and high quality knowledge tool could be very beneficial for research involving different educational methods for patients

2.4.3. Format of Validated Questionnaires

With a range of 15 to 29 total questions and the potential to take from 6.5 to 20 minutes to complete, there are many differences in the validated tools. The MCQ style of question seems to be the most popular, perhaps due to its ease of quantification upon data collection and the ability to compare results. The elimination of potential guessing of answers needs to be considered when using this style of question. Often the correct answer is easy to choose without specific knowledge of the topic. Zeolla *et al.*, Obamiro *et al.*, and Magon *et al.* all included a subgroup of participants in their study from the general public. [2, 3, 103] Such groups had no history of anticoagulant use

and so were expected to serve as a negative control for the studies. The likelihood of randomly selecting a correct answer will increase with fewer response options available. [118]

There has been some criticism toward the inclusion of a “I do not know” response option in a questionnaire in the past. There are a few theories as to why participants would select this option rather than expressing their true opinion or answering honestly. Firstly, participants could choose this option due to a lack of understanding of the question. [119] Secondly, to avoid thinking and/or committing themselves to the survey. [120] Finally, when the test exceeds their motivation or ability. [121] However, the use of closed-ended questions is advantageous for statistical analysis, which is valuable in scientific research and also facilitates automation. [122]

2.4.4. Topics Covered in Validated Questionnaires

The subjects covered in each questionnaire are similar. For example, all tools include basic drug information, drug-drug interactions, and laboratory monitoring. Most authors approached the decision with an initial review of the current literature and protocols used in practice for OAC counselling. [1, 3-5] Some research teams also used a panel of healthcare professionals with experience in the area to come to an agreement on content of the questionnaires. [1, 2, 4] Unfortunately, there is no single, definitive standard document that can be used to assist patient education of DOACs. Two leading international bodies: the EHRA and the iPACT have both produced documents with recommendations on the topic. [13, 72]

The EHRA guidelines recommended the following topics for inclusion: indication, mechanism of action, missed doses/dosing errors, bleeding/trauma, drug interactions, informing a HCP before procedures, when to contact a HCP, and monitoring. [13] The iPACT guidelines recommend: benefits of treatment, risks of treatment, how to prevent complications, how to act in an emergency/Patient Alert Card, reason for taking DOAC, duration of therapy, food intake, drug interactions, side effects, and reasons why therapy may be suspended e.g. surgery. [72] Questionnaires should be reviewed prior to their use to ensure they contain all of the essential knowledge points in order to be effective.

The indication, or reason for taking the anticoagulant, is only included in the AKA, KODOA-test, the JAKQ and JAKQ-VTE. The mechanism of action of the OAC was covered by the KODOA-test only. What to do for missed doses and information regarding informing a HCP of OAC status before procedures, or reasons why therapy may be suspended was addressed in the AKA, AKT, JAKQ, JAKQ-VTE and KODOA. Side effects/risks of therapy, drug interactions, and monitoring were covered in all of the questionnaires. However, the benefits of treatment were only mentioned in the AKA. How

2. Knowledge Questionnaires Literature Review

to prevent complications was only incorporated into the AKT and AKA. How to act in an emergency/patient alert card was mentioned in the AKA, KODOA, JAKQ-VTE, JAKQ and AKT. Duration of therapy was found in the KODOA and AKT. Food intake was only included in the AKA and OAK. However, it should be noted that there is little detail given in the OAK description as only 5 basic content areas were outlined. Therefore it is difficult to determine what specific information is included. [1-6]

None of the knowledge tools had patient input in the initial stages of content formation. The most common method used was analysis of existing literature and receiving input from experienced healthcare professionals. A user-based design, with inclusion of relevant patient groups to gain their perspective could be useful when creating the questionnaires. This would ensure end-user needs are met. Most researchers included patient groups once the tool was initially create, to allow for adaptation at the validation stage. It could be argued that patient groups would be less knowledgeable on the topics required for their own education, but early inclusion would help to improve satisfaction for users.

2.4.5. Validation Methods

One could argue that the more robust a validation process of a tool, the more likely it is to be effective and useful in its indication. It is interesting to see that the AKA was initially reviewed by just two independent experts in item writing, in contrast to the panel of 27 HCPs involved in the JAKQ validation. [1, 4] As each new tool was produced and validated in this research area, more authors used the opinion of HCPs with expertise in the topic during content validation. This would likely lead to a more effective tool and one that would be used by HCPs following validation. Consensus from an expert committee is recommended to judge whether the items appropriately measure the construct intended to assess, for example: the questions were clear and easy, you would like to use this questionnaire for future assessments, etc. [114] There is no consensus on the numbers required for questionnaire validation, with guidelines for the respondent-to-item ratio ranging from 5:1 to 30:1, and a suggestion that sample sizes of 50 should be considered very poor, 100 as poor, 200 as fair, 300 as good, 500 as very good, and 1000 or more as excellent. [114]

2.4.6. Quality of Validation Studies

2.4.6.1. Scope and Purpose

All studies have a clearly defined objective at the beginning of the paper. [1-6] This helps the reader to have an understanding of the goal of the research from the outset.

2.4.6.2. Stakeholder Involvement

Each of the studies, with the exception of Koniecynska *et al.*, involved healthcare professionals with experience in the area to validate their instruments. [1-6] The inclusion of experts in the area, not on the research team, uses the judgemental method for evaluating test content, whether the content of a test is scrutinised by subject matter experts. This adds value to a validation study. [123] All studies used participants from the target population to assess their interventions. [1-6]

2.4.6.3. Rigour of Development

Neither Briggs *et al.* nor Koniecynska *et al.* mentioned any limitations associated with their study. Furthermore, the validation methods used for both studies seemed less rigorous than the methods outlined in Zeolla *et al.*, Obamiro *et al.*, Desteghe *et al.*, and Metaxas *et al.*. [1-6]

2.4.6.4. Clarity of Presentation

All studies clearly presented their findings and recommendations. [1-6]

2.4.6.5. Applicability

The applicability of the findings of each study was presented by the authors and the intended uses of the questionnaires were noted throughout the studies.[1-6]

2.4.6.6. Editorial Independence

It is beneficial for readers to know of any potential conflicts of interest and funding to maintain the integrity of a study. [124] Briggs *et al.* does not address either in their research paper. [1] Desteghe *et al.* and Metaxas *et al.* mentioned both (conflicts of interest and funding), even if none existed. [4, 6]

2.4.6.7. Overall Assessment

Overall, the quality of the studies are limited by their small sample size (ranging from 32 to 466 participants), and therefore the lack of generalisability of the results. There was a clear difference seen in the methods of analysis used in Briggs *et al.* and Koniecynska *et al.*. [1, 5] For instance, the Rasch analysis method used by Briggs *et al.* and the validation method by Koniecynska *et al.* seemed to lack the detail of content validity, construct validity, test-retest reliability, sensitivity testing and discriminatory potential which are included in the other studies. [2-4, 6] Each study requires further research to enhance the applicability of the evidence and strengthen the questionnaires. [1-6]

2.4.7. Validated Questionnaires Used in New Settings

The translation and re-validation of a questionnaire in a new population is seen in the I-AKT and the Brazilian OAK test. [103, 104] This is potentially beneficial as it allows for the comparison of future interventions and a meta-analysis of common data. The JAKQ has been used in several studies in testing the efficacy of various interventions. [82, 84, 105] These studies show the potential for tools such as the JAKQ, AKT, and OAK test, for use in real-world settings in enabling the provision of healthcare. Other validated questionnaires may need to conduct similar research to further strengthen the tool and encourage its use.

2.4.8. Documented Questionnaires With No Specific Validation

Both Smith *et al.* and Lane *et al.* made use of questionnaires to assess patients' knowledge of their condition and oral anticoagulant which had not yet been fully validated. [90, 110] As seen in the previous validated questionnaires, the process of official validation is rigorous and ensures maximum efficacy when used in a study. The use of a non-validated questionnaire can weaken a study and limit its impact in the field of research. Formal validation is required to strengthen the study and ensure the questionnaire effectively evaluates patient knowledge.

2.5. CONCLUSION

Following a review of the current literature, six validated knowledge tools are available to assess patient knowledge of oral anticoagulants. The topics covered and their intended uses in all questionnaires are relatively similar. The main differences seen are in the type of anticoagulant covered and the number and style of the questions. The older questionnaires appear to have more items and take more time to complete, whilst focusing primarily on warfarin patients. [1-3] Tools published since 2016 are more concise and include DOACs, as their prescribing frequency has steadily increased since 2014. [4-6, 125]

The validation of translated knowledge tools allows for comparison of results between populations. [103, 104] The use of the tools in studies evaluating educational interventions provides further evidence of their efficacy and reliability. More research is required on the effectiveness of knowledge tools and their relation to patient outcomes.

3. Pilot Study for Validation of the Knowledge Questionnaire

3.1. BACKGROUND

DOACs are commonly prescribed around the world, having recently overtaken warfarin as the oral anticoagulant of choice for several cardiovascular indications, such as stroke prevention in AF. [13] They are also used in VTE management, and have been shown to be non-inferior to warfarin in randomised controlled trials in terms of their efficacy. Additionally, they may have advantages over heparin/warfarin treatments in terms of safety. [126]

Despite their advantages, DOACs are still classified as high risk medicines by the Institute of Safe Medication Practices. [127] Since their authorisation in 2016, there has been an increase in the number of patients presenting in emergency departments with bleeding-associated complications, most crucially intracranial and gastrointestinal bleeding. [126] A strong correlation exists between increasing age and risk of major bleeding. [128, 129] We know that AF incidence increases with age, which can then lead to DOAC prescribing for the reduction of stroke risk. [130] Renal impairment is also a well-known factor to increase the risk of bleeding for each DOAC. [131] The prevalence of chronic kidney disease, or CKD, rises dramatically with age. [132]

In 2016, the State Claims Agency in Ireland featured DOACs in the top twenty most common medicines accounting for medication incidents reported in Irish hospitals. [60] The report acknowledged that the options for managing DOAC induced bleeds at that time were extremely limited. Currently two reversal agents are licensed in Ireland: idarucizumab and andexant alfa. [54, 133] Idarucizumab is licensed for the rapid reversal of dabigatran anticoagulant effects. [133] Andexant alfa is licensed for the reversal of apixaban and rivaroxaban anticoagulant effects, where reversal is needed due to life-threatening or uncontrolled bleeding. [54] Prothrombin complex concentrate (PCC) is a non-specific prohaemostatic agent which has also been used for DOAC reversal. [134]

Medication adherence (taking drugs as prescribed) and persistence (continuation of therapy) in DOACs is especially important due to their short half-lives and lack of routine monitoring. [135, 136] The medication is cleared from the body within 12-24 hours. Patients will no longer be protected against stroke in AF, or their treatment will be ineffective in VTE, if doses of DOACs are missed. [137] Patients therefore require comprehensive medication counselling from healthcare professionals when being initiated on DOAC therapy, with confirmation of their understanding.

Due to high levels of workload currently placed on healthcare professionals, finding time to efficiently educate and ensure patient understanding is not always feasible. [74-76] Oftentimes, patients are provided with manufacturer-produced information leaflets filled with generalised counselling points. These materials are not necessarily easy to digest and can use medical jargon. [138] Knowledge deficits in patients can go unaddressed, introducing risk. [139]

Knowledge questionnaires for those taking OACs have risen in popularity in recent times. [1-6] They could be a solution to improving the safe and effective use of DOACs by allowing healthcare professionals to provide tailored education to each individual patients and to reassess their knowledge levels after education. [12] There is room for an English language DOAC knowledge questionnaire to be developed and trialled in the Irish healthcare system.

3.2. AIMS AND OBJECTIVES

3.2.1. Aims

The study aim was to design and trial English language knowledge tests for patients taking DOACs.

3.2.2. Objectives

- To trial and initiate validation of the JAKQ for DOACs, with any modification prompted in the course of the trial
- To develop a variant of the JAKQ suitable for VTE patients using DOACs

3.3. METHOD

3.3.1. Study Design and Setting

The trial of the knowledge questionnaires to be used in the study in Tallaght University Hospital's (TUH) Atrial Fibrillation Clinic. Initially, the questionnaires were to be used in AMU of TUH and in community pharmacies also but this was prevented by Coronavirus Disease 2019 (COVID-19).

3.3.2. Ethical Considerations

This study was approved by Tallaght University Hospital/St James' Hospital Joint Research and Ethics Committee (JREC Ref 2019-11 Chairman's Action (10)). Approval was granted on the 12th of November 2019. Minor amendments were made to the study design to allow for patient telephone calls to be conducted due to COVID-19 research obstructions. These updates were granted approval by the JREC committee on the 21st of October 2020 (Ref 2020-10 Amendment (14)). Participants of each phase were also informed about the confidentiality of their responses and anonymity in the presentation of data for the final report of the study.

3.3.3. Outcomes

- Knowledge questionnaire scores
- Qualitative data on the questionnaires

3.3.4. Intervention Development

The JAKQ was used as the starting point for the questionnaire development, as this Dutch language questionnaire had been validated previously among 466 patients. [4] The JAKQ had originally been translated to English, but this version has not yet been validated. This can be found in Table 2-1. As JAKQ had a segment focused on patients with AF and their knowledge surrounding the condition, a version was developed that would be appropriate for patients with VTE. This JAKQ for VTE was modelled from the JAKQ and also took inspiration from a Polish research group who had previously modified and created the JAKQ-VTE. [5] Both questionnaires were assessed by the research team in TUH. The sections of the JAKQ related to warfarin therapy were excluded for this study, as DOACs were the sole focus due to their increasing popularity for use in oral anticoagulation.

Background knowledge was gained on the subject of DOACs through research and the information was compiled. This supplemented the researchers' existing knowledge following on from her previous BSc. (Pharm.) and MPharm. degrees. Various resources available in both Ireland and globally were used to enable the development of good quality work. Examples of resources used include: the Irish Pharmacy Union (IPU) website [140], a group who consistently develop educational content for pharmacists; the National Medicines Information Centre (NMIC) [141], who seek to promote the safe and effective use of medicines through bulletins and publications; and the individual SmPC for each DOAC found via the Health Products Regulatory Authority (HPRA). [142-145] A review of the published literature and anticoagulation clinic documentation was performed to identify educational content areas typically addressed in pharmacist-managed anticoagulation clinics. The EHRA and iPACT guidelines were used as valuable resources during this process. [12, 13, 72]

Interviews with anticoagulation pharmacists on the research team were conducted to gain additional insight into their practices and they provided educational content areas that they felt were essential for patients to understand. Furthermore, the information provided by the pharmacists delineated common misconceptions or misunderstandings that patients have concerning their anticoagulant therapy and AF condition. Through rounds of feedback, the essential knowledge points were finalised. Resources on the development of healthcare materials produced by the National Adult Literacy Agency (NALA) were consulted to guide the format and wording of

the tool. [146] A course conducted by NALA in designing educational material for patients was also completed in TUH. The SMOG readability formula was used to ensure readability amongst the general population. [147]

3.3.5. Participants for Content Validation Phase

Nine healthcare professionals consisting of four doctors, three pharmacists and two nurses were recruited. HCPs were from outside the research team with experience and expertise in AF, VTE and the use of DOAC medication.

3.3.6. Content Validation

A panel of 9 healthcare professionals with experience and expertise in DOACs, AF and VTE were recruited to join the study. Participants were required to validate the content of the questionnaire based on their experience in the education of patients taking DOACs. This panel included three pharmacists, two nurses and four doctors. The participants were given a copy of the questionnaires and asked questions such as: “Do you feel the questionnaire covers all essential knowledge points for patients taking DOACs?”, and “Is the language use appropriate for patients, in your opinion?”. There were spaces left for participants to give their comments on each individual question also. Feedback on the questionnaire was provided by the recruited HCPs. HCPs were given as much time as they needed to read through the questionnaire as the majority of this research was conducted via email. One HCP gave their feedback via telephone call. Initially, this phase of the research was planned to be conducted in person, at a location convenient to the participant. However, due to COVID-19, this was amended and participants were permitted to complete the study in their own time. The responses were reviewed by a member of the research team and collated. Adapted forms of the questionnaires were produced which took into account the feedback from the panel. This version was shared with the research team for further review. A total of three iterations of the questionnaire were produced during this process, which eventually led to the version used in the pilot study.

3.3.7. Participants for Pilot Study Phase

Ten adult patients (> 18 years) attending TUH AF clinic, with capacity to provide informed consent and not simultaneously participating in another research project were recruited. Participants were required to have AF and be taking a DOAC (not necessarily for the first time).

3.3.8. Pilot Study Validation in a Patient Cohort

3.3.8.1. Recruitment in Person

Eligible patients attending TUH AF Clinic were invited to participate in the study. Patients were asked to read the participant information leaflet and fill out the consent form if they were happy to do so. The researcher then outlined the process for questionnaire completion and participants were provided with the questionnaire.

The questionnaire for VTE patients could not be piloted as this would have involved recruitment throughout the AMU in TUH, and this was precluded by COVID-19 restrictions.

As many of the clinic consultations were conducted via phone call, by hospital doctors only, the numbers of potential patients to be recruited were reduced significantly. Without being able to speak to patients directly, the AF clinic pharmacist recruited any eligible patients in clinic and the researcher phoned patients to confirm their participation.

3.3.8.2. Recruitment via Telephone Consultation

Some patients were recruited over the phone by the researcher in an attempt to increase participant numbers. Their details were provided by AF clinic pharmacists and doctors during their clinic appointments who had originally discussed the study with them and asked if they would take the call.

3.3.8.3. Questionnaire Completion

Participants recruited by the researcher in clinic filled out the questionnaires in the presence of the researcher. Completed questionnaires were retained for data collection. Those recruited in clinic by the AF pharmacist were called by the researcher to confirm their participation, and were sent out a pack containing a letter of invitation to the study, a participant information leaflet, a consent form, and the JAKQ.

Participants recruited via telephone were sent out the same pack as above. Patients were asked to read the participant information leaflet and fill out the consent form if they were happy to do so. Further questions were encouraged and contact details were provided throughout the documentation.

Participants were invited to complete the JAKQ over the phone with a researcher. However, most participants were happy to complete the JAKQ in their own time. The completed documentation was returned to the researchers via a freepost envelope.

The think aloud method was used with one participant in the AF clinic where they answered the questionnaire while talking through any parts of the questionnaire they found difficult and giving any feedback in general. [148]

3.3.9. Incorporation of Pilot Study Results

Following the pilot study of the validation of the questionnaire, any feedback or insight gained was used to further modify the knowledge questionnaire and produce Version 3.0.

3.3.10. Statistical Analysis

The quantitative data collected was analysed using the IBM SPSS version 26.0 (IBM Analytics, New York, USA) and Microsoft Excel software, version 16.45 (Microsoft Corporation, Washington, USA). Descriptive summary statistics were generated in SPSS to describe the sample characteristics.

Content validity analyses the extent to which the items on the questionnaire are representative of the entire theoretical construct the questionnaire is intended to assess. [149] The panel of expert HCPs were tasked to evaluate the content validity of the questionnaire. HCPs were asked if the questions' meaning was clear or if there was any ambiguity, if there were any other essential points to include in the questionnaire that were not currently included, if the language used was likely to be understood by patients in the target population, and if they had any other comments.

Face validity is the extent to which a questionnaire seems to measure what it intends to measure. [150] Initial piloting of face validity was undertaken on a small scale using feedback provided by each patient who completed the questionnaire. The think aloud method was undertaken with one patient in which they were invited to read through the questionnaire and tell the researcher any thoughts they had surrounding the tool throughout. [148]

3.4. RESULTS

3.4.1. Content Validation

Many of the comments were regarding the medical jargon used in the questionnaire. Some examples include:

- Arrhythmia [Dr 1]
- Heart Failure [Dr 1]
- Exacerbates [Dr 1]
- Cerebral Infarction [Nurse 2/Pharmacist 1]
- DOACs [Pharmacist 1]

Some of the language used seemed ambiguous or could be improved. For example:

- “I can detect AF by taking my pulse regularly” – “This is ambivalent and misleading. It implies the patient can, and may be at fault for ‘failing’ to diagnose.” [Dr 1], “Explain how regularly.” [Nurse 2]
- “Avoid the use of brand names, use ‘paracetamol’ instead.” [Dr 1]
- “Answers to Q2 missed doses of DOACs in AF is not clear.” [Dr 4]
- “The correct answer is very negative.” [Nurse 1]
- “I should always take my blood thinner (as prescribed).” [Nurse 1]
- “Which painkillers may I take (when taking a blood thinner).” [Nurse 1]
- “Q2 Missed dose very confusing, patients should be told how to manage a missed dose, not make a guess at it.” [Nurse 1]
- “Q2 Missed dose language is complex and should be simplified.” [Pharmacist 1]
- “Patients should show their alert card to all healthcare professionals not just GP and specialist.” [Pharmacist 1]
- “The language needs to be easy to understand at a basic entry level – as per NALA guidance and experience with SMOG testing.” [Pharmacist 2]
- “Some of the focus could be changed to being more patient centred.” [Pharmacist 2]
- ““Paracetamol containing pain relief” rather than “medication based on paracetamol”.” [Pharmacist 3]
- “Remove “in order to” and replace with “to”.” [Pharmacist 3]

Other feedback considered the purpose of certain questions.

- “Q1.5: Medication cannot prevent AF permanently, as the arrhythmia will increasingly occur with ageing, even when taking medication.” – “I don’t see the objective of this question. Suggest more simply: Medication can greatly reduce the risk of serious stroke in people with AF.” [Dr 1]

Finally, some points were raised about topics not covered in the questionnaire:

- “Would suggest a question to further assess patients awareness of other important lifestyle risk factors, include alcohol excess or sedentary lifestyle.” [Dr 3]
- “Suggest including questions about risk for AF, sleep apnoea, hypertension, exercise.” [Dr 4]
- “Consider including Aspirin, as some patients may need to take it.” [Dr 4]
- “Why just overweight, what about alcohol and smoking? If patients are going to make lifestyle changes now is the time!” [Nurse 1]
- “Consider including another question about duration of DOACs in the setting of AF? Some patients may be unaware that it is usually lifelong treatment.” [Pharmacist 1]
- “Consider including ‘DOACs should be used for at least 3 months or longer after diagnosis of DVT/PE as directed by your doctor’.” [Pharmacist 1]
- “Consider adding a question about what to do in the event of major bleeding e.g. coughing up blood, as patients should be aware that they need to access medical help ASAP.” [Pharmacist 1]

Positive feedback was welcome:

- “Overall excellent questionnaire.” [Dr 3]
- “Well done on great questionnaires.” [Pharmacist 2]

Version 2.0 of the questionnaire was then created based on these comments, as well as back and forth discussion in the research team, ready to be used in the pilot study with AF patients.

Version 1.0 and version 2.0 of the questionnaire can be found in Questionnaires.

3.4.2. Pilot Study of the Validation

The questions most frequently answered correctly were questions 4, 8, 10, 14, 16 - 100% (10/10) of participants got these questions right. The subjects of these questions were: the possible effects

of AF, factors that increase the risk of AF, when to take the DOAC, what patients should do if they experience a major bleed, and the importance of taking the DOAC at the same time every day. Questions 5 and 9, the majority of patients (9/10 or 90%) got correct - concerning DOACs reducing the risk of stroke, and why anticoagulants are often prescribed for patients with AF. Question 7, relating to the effects of being overweight on AF risk, was answered correctly by 80% (8/10) patients, while 70% (7/10) of participants answered questions 1, 11, 13, and 15 correctly. The subjects of each of these questions were the meaning of AF, possible side effects of DOACs, what to do in the case of minor bleeds, and what to do if you need an operation. Two of the participants did not know the answer to question 11. Thirty percent (3/10) of patients selected "I do not know" for question 13 also. Question 2, regarding whether the patient will always feel symptoms of AF, was answered correctly by 60% (6/10) patients.

Only 50% (5/10) of participants chose the right answer for question 12, regarding which painkillers are safe to take with DOACs. The option "I do not know" was chosen by 30% (3/10) of participants for this question.

Question 17 was most frequently answered incorrectly, with 90% (9/10) of participants choosing the incorrect answer. This question related to what to do if a dose of DOAC is missed. Question 3 was answered incorrectly by 40% (4/10) of participants, with 50% (5/10) choosing the option "I do not know". This question asked participants how they could detect AF.

Finally, 20% (2/10) of participants chose the wrong answer for question 6 - if the patient should go to the doctor each time they feel AF. However, 40% (4/10) patients did not know the answer to this question.

Table 3-1: Summary of Questionnaire Responses

Question	Proportion of Participants (n = 10) Answering Correctly	Proportion of Participants (n = 10) Answering Incorrectly	Proportion of Participants (n = 10) Answering “Don’t Know”
1	7 (70%)	2 (20%)	1 (10%)
2	6 (60%)	1 (10%)	3 (30%)
3	1 (10%)	4 (40%)	5 (50%)
4	10 (100%)	0	0
5	9 (90%)	1 (10%)	0
6	4 (40%)	2 (20%)	4 (40%)
7	8 (80%)	2 (20%)	0
8	10 (100%)	0	0
9	9 (90%)	1 (10%)	0
10	10 (100%)	0	0
11	7 (70%)	1 (10%)	2 (20%)
12	5 (50%)	2 (20%)	3 (30%)
13	7 (70%)	0	3 (30%)
14	10 (100%)	0	0
15	7 (70%)	3 (30%)	0
16	10 (100%)	0	0
17	1 (10%)	9 (90%)	0

During the think aloud method conducted with one participant, they did not realise that there was only one correct option per question, and chose two options for Q1 “what is AF?”: “A condition where the heart beats irregularly and often faster than normal”, and “a disease of the blood causing blood clots in the heart.” The patient reasoned the later choice: “because you could get a blood clot in your heart as well”.

The participant said he did not understand question 5 “DOACs can” followed by a list of potential therapeutic benefits. Once the researcher showed him which of his medicines was a DOAC and what DOAC meant, the participant was able to answer the question correctly.

For question 8 regarding factors that can increase the risk of AF, the participant initially was confused by which option to choose. They said “I don’t smoke so I’m not sure”. There was a lack of understanding that the question wasn’t necessarily about their lifestyle but general measures. They answered the questions correctly once this was explained.

For “what to do in the case of a minor bleed”, the patients wasn’t certain of the answer, commenting “I wouldn’t go to the hospital, and I wouldn’t stop taking it...”. They still chose the correct option for this question. Whilst filling out the questionnaire, but not via the talk through

method, one participant commented on the ways to detect AF. They noted that they can detect AF through their Apple watch.

3.4.3. Incorporation of the Pilot Study Results

Version 3.0 of the questionnaire was proposed based on the information gained during the pilot study. The changes made include highlighting the questions in bold to help patients differentiate between questions, and attempting to highlight the fact that there is only one correct answer by only emphasising “ONE” in bold. The term DOACs was defined earlier in the questionnaire to avoid any misunderstanding. In question three, “what can I do to detect AF?”, we have added the use of a device such as a smart watch to potentially detect AF, as suggested by a patient. No further amendments were made. Participant’s difficulties in answering question 3, 6 and 17 highlights the areas requiring further education amongst the patients.. Version 3.0 of the questionnaire for AF patients can be found in Table 2-7.

3.5. DISCUSSION

3.5.1. Content Validation

The panel of HCPs with experience and expertise in DOACs, AF, and VTE provided significant constructive criticism and feedback for the questionnaire. As the English version of the JAKQ was a direct translation, the majority of the feedback suggested improvements to language and the use of more unambiguous phrases. It was helpful to have any medical jargon flagged, and each of the words recommended were changed to simpler terms.

For example:

- Arrhythmia = AF
- Heart Failure = Heart Muscle Disease
- Exacerbates = Increases the Risk
- Cerebral Infarction = Stroke
- DOACs = Direct Oral Anticoagulants
- Hypertension = High Blood Pressure

A pamphlet developed by NALA on writing and design tips for information leaflets was also used to include plain English. This document contains a list of common medical jargon terms used and alternatives to replace them. [151] Examples include: hypertension = high blood pressure, and

medication = tablets, injections (specify). Font size, line spacing and typeface choice were as per the NALA guidance. [151]

Based on the feedback from HCPs and review of NALA guidance, the following amendments were made to the questionnaire:

- “I can detect AF by taking my pulse regularly” changed to “I could possibly detect AF by taking my pulse twice a day for two weeks and noting the result”.
- “Paracetamol containing products e.g. Panadol” changed to “Painkillers containing paracetamol”.
- “I should still take that dose, unless the time till my next dose is less than the time after my missed dose” changed to “I should ask my doctor, nurse, or pharmacist, or read the leaflet that comes with my DOAC”.
- “I should always take my blood thinner” changed to “I should always take my DOAC as prescribed”.
- “Which painkillers may I take” changed to “Which painkillers are safe to take with DOACs”.
- “My blood thinner comes with an alert card which I have to show to my general practitioner and specialist” this question was removed.
- “In order to” changed to “To”.

Also, the suggested addition of topics was taken on board. Such suggestions included:

- An additional question regarding lifestyle factors such as alcohol intake, smoking, and high blood pressure.
- A question about what to do in the event of major bleeding was added.

The suggestion of adding questions about lifestyle factors was interesting because during the validation process of the KODOA-test, the expert panel selected 15 out of 45 compiled items to be important for knowledge of DOACs – none of which included lifestyle factors. [6] It is possible that the choice of questions included in the knowledge questionnaire would differ between HCP panels.

The above examples show the impact of content validation on the questionnaire. Conducting this process was extremely valuable and allowed the questionnaire to take on a more effective, readable and understandable form. If any feedback was contradictory, the research team discussed the various options and through back and forth editing, the final version was produced.

3.5.2. Pilot Study of the Validation

Atrial fibrillation is a chronic condition which requires patients to have an acceptable knowledge level regarding their condition and its treatment. [152-154] This level of knowledge allows for

patient involvement and shared decision making, which improves care by identifying personal goals and aspects of disease impact. Such aspects can be missed by clinical outcome measures alone. [155] Equally with VTE, there are important knowledge gaps in patients concerning VTE in general and the associated oral anticoagulation therapy. [5]

Although our pilot study was conducted in small numbers, it still gave an insight into potential knowledge gaps in the Irish population of patients with AF taking DOACs.

It was clear that some knowledge gaps exist in the participants taking part in the study. Only one of the patients completed the questionnaire prior to their consultation with their doctor, therefore standard patient education had been delivered in nine out of ten patients. Patient 7, who completed the questionnaire prior to counselling, was the only patient to select “I don’t know” for question 1. They were also the only patient to select the incorrect answer for question 2. This participant had a total of 12 out of 17 questions correct, with two “I don’t know” responses. Patient 7 was the only participant to select the correct option for question 17. However, many of the patients had a significant gap in time between their consultation in the AF clinic and completing the questionnaire, due to postal delays. As the sample size was too small, one could not determine the differences between already educated and non-educated participants’ responses.

Table 3-1 shows the summary of questions answered incorrectly, correctly, or “I don’t know” by participants. Five out of the total 17 questions were answered correctly by all patients. All patients had a high level of understanding of the possible effects of AF, the factors that can increase the risk of AF, when to take the DOAC, what to do in the event of a major bleed, and to take the DOAC at the same time every day.

There were further eight questions in which the majority (over 60%) of patients answered them correctly. This means that 13 out of 17 questions were answered correctly by more than 50% of patients.

Four of the questions were answered incorrectly, or answered “I don’t know” by less than or equal to 50% of participants. The subjects of these questions included which painkillers were safe to take with DOACs, how to detect AF, what to do if a dose of DOAC is missed, and whether the patient should go to the doctor each time they feel AF. Question 3 had the most amount of “I don’t know” responses, with 50% (5/10). This item related to what the patient can do to detect AF.

By carrying out the think aloud method with one patient, further points were disclosed regarding the questionnaire. The fact that the patient wasn’t initially aware that only one option was to be

chosen per question meant perhaps it had not been made clear enough by the layout or the instructions provided. At the beginning of the questionnaire, participants were told to select only one answer per question. It is possible that the patient had trouble differentiating each question due to the layout or lack of bold font used.

Also, the phrase DOACs may need to be defined more clearly, or it should be explained to patients which of their medications is a DOAC. This could clear up any confusion with the questions using the term DOACs.

It could be beneficial to include the use of smartphones and smartwatches to detect AF, as noted by one patient. This method of screening has been acknowledged by the EHRA, where downloadable healthcare apps have the potential to be used widely and for unrestricted periods of time. [156]

Similar studies conducted have shown that patients have a poor level of knowledge of their condition (AF/VTE) and its treatment based on survey results. [4, 5] McCabe *et al.* reported that 46% of patients with AF knew that it leads to an increased risk of stroke. [157] Lane *et al.* and Lip *et al.* revealed that only 49% and 63% of patients respectively knew that their condition was called AF. [110, 158] Likewise, one-fifth of participants had never heard of either DVT or PE in a study produced by Le Sage *et al.*. [159] The validation of the questionnaire developed throughout this study has the potential to be beneficial to healthcare workers and patients alike, as shown in a study trialling the JAKQ for providing individualised counselling to patients. [82] The questionnaire's proposed use is to determine patients' baseline knowledge, then to reveal any further misunderstandings following counselling by HCPs. It is hoped that this would optimise the efficiency of the education provided.

3.5.3. Limitations of the Study

Participant numbers were not high enough to validate the questionnaire as previously intended. Prior to COVID-19, participants were to be recruited throughout Tallaght University Hospital and in nine community pharmacies across Ireland. The impact of the pandemic meant that the questionnaire for VTE patients could not be trialled at all. Similarly, the population of non-cardiovascular patients in primary care approved for evaluation of the questionnaires' discriminatory potential could not be approached. This is recommended for future work and would strengthen the questionnaire entirely. The formal validation of the questionnaire under a variety of conditions is intended and would further improve the standard of the tool. We chose to use closed-ended answer formats for the questionnaire, including a "I do not know" option, to

eliminate guessing. However, there is also a risk that patients would be able to answer even if they do not actually understand the question being asked. [160] The proposed format is used in this questionnaire as to have an automated screening method prior to counselling. The comparison of results before and after counselling is possible when using closed questions.

3.6. CONCLUSION

The questionnaire detailed in this study covers the essential knowledge points outlined by the EHRA for patients taking DOACs. [12] The questionnaire has undergone preliminary analysis of its content among a cohort of HCPs with experience in the areas of DOACs, VTE and AF. The questionnaire results are promising and show that it could be a useful tool to discover patients' knowledge gaps to aid education. Further research is needed to validate the questionnaire for AF patients in the Irish population and to conduct face validation, test-retest reliability, discriminatory potential and sensitivity testing, and principal component analysis to determine construct validity and internal consistency. The questionnaire for VTE patients must be validated appropriately also.

4. Electronic Education for OAC Patients: A Literature Review

4.1. BACKGROUND

This chapter will outline a review of the current literature associated with electronic patient education methods for patients taking oral anticoagulants.

There have been many attempts at creating mHealth technologies for the management of chronic conditions in recent times, primarily due to their accessibility, potentiality for personalisation and ease of implementation. The World Health Organisation has acknowledged the potential of mHealth interventions to “transform the face of health service delivery across the globe.” [161]

Although no official definition of mHealth exists, it is categorised under eHealth. The Global Observatory for eHealth (GOe) defined mHealth or mobile health as “medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants (PDAs), and other wireless devices.” [161] mHealth offers the potential to improve access to healthcare and health-related information that is validated and provided by a reliable source.

Mobile devices can allow for the collection of data in real time and are increasingly common, enabling the analysis of multiple patient behaviours in various contexts by researchers and therefore inform the development of interventions to prompt behaviour change. [162] Behavioural health interventions supported by technology are designed to engage patients in health behaviours that prevent or manage illness, and they have led to fundamental changes in health practices. [163] In addition to enabling more frequent communication between healthcare professionals and patients, these technology-supported tools also encourage shared decision-making practices, and improve patient engagement with health-positive behaviours. [164, 165]

With all of the potential benefits of these electronic tools, it is important to investigate the degree to which these technologies include best content and have been evaluated for their effectiveness. There are concerns that these apps being developed do not incorporate evidence-based information and lack rigorous testing to prove their efficacy. [166, 167]

4.1.1. Importance of the Review

DOACs are high risk medicines as they treat high risk conditions, so it is essential to effectively educate patients about their anticoagulation therapy to ensure the important counselling points

were understood. This review will examine randomised controlled trials (RCT) and quasi-controlled trials using electronic educational tools as interventions for patients taking OACs or AF patients. Reviewing such will benefit the development of the electronic educational video tool proposed by the research team.

4.1.2. Aims & Objectives

1. Conduct a literature review of RCTs and quasi-controlled trials for electronic educational interventions used for patients taking OACs or AF patients.
2. Perform an analysis of the interventions used in included trials.
3. Complete a risk of bias assessment of included studies.

4.2. METHODS

4.2.1. Inclusion Criteria of Studies

4.2.1.1. Types of Studies

Randomized controlled trials (RCTs) and quasi-randomised controlled trials in which patients were assigned to groups by methods other than true randomisation (e.g. alternate assignment) were included. Studies published in English that met the selection criteria were included. Studies were excluded that did not have a control group or adequate information to assess the effect of the intervention.

4.2.1.2. Types of Participants

Studies of patients on warfarin or DOAC treatment were used, including studies for AF patients. Studies focused on OAC education for healthcare professionals were excluded.

4.2.1.3. Types of Interventions

This review focused on electronic, educational interventions for patients taking OACs or AF patients.

4.2.2. Search Strategy for Identification of Studies

Electronic searches of the databases were conducted using PubMed NLM, EMBASE, and Google Scholar to identify potentially relevant literature. Study titles and abstracts were initially screened to filter out relevant materials. The search was conducted between May and November 2020. Boolean operators (AND, OR) were utilised in the search strategy to effectively combine concepts. The search results were limited to English-language only.

The literature search strategy is outlined below.

Table 4-1: PubMed (MEDLINE) Literature Search Strategy

PubMed (MEDLINE) Literature Search Strategy		
#1	("warfarin"[Title/Abstract]) OR "coumadin"[Title/Abstract]) OR "coumarin"[Title/Abstract]	35,562
#2	anticoagula*[Title/Abstract]	95,951
#3	"direct oral anticoagula*"[Title/Abstract] OR "doac*"[Title/Abstract] OR "novel oral anticoagula*"[Title/Abstract] OR "noac*"[Title/Abstract] OR "apixaban"[Title/Abstract] OR "rivaroxaban"[Title/Abstract] OR "dabigatran"[Title/Abstract] OR "edoxaban"[Title/Abstract]	12,156
#4	#1 OR #2 OR #3	119,780
#5	#2 OR #3	99,143
#6	("smartphone"[Title/Abstract]) OR "mobile"[Title/Abstract]) OR "mobile health"[Title/Abstract]) OR "cell phone"[Title/Abstract]) OR "iphone"[Title/Abstract]	105,248
#7	("computer"[Title/Abstract]) OR "laptop"[Title/Abstract]	217,493
#8	("digital tablet"[Title/Abstract]) OR "ipod"[Title/Abstract]) OR "ipad"[Title/Abstract]	1,631
#9	("internet"[Title/Abstract]) OR "application"[Title/Abstract]) OR "online"[Title/Abstract]) OR "software"[Title/Abstract]) OR "website"[Title/Abstract]) OR "electronic"[Title/Abstract]) OR "electronic health"[Title/Abstract]) OR "e health"[Title/Abstract]) OR "technology"[Title/Abstract]) OR "intervention"[Title/Abstract]) OR "virtual health"[Title/Abstract]	2,096,266
#10	(educat*[Title/Abstract]) OR "knowledge"[Title/Abstract]) OR understand*[Title/Abstract]) OR "drug information"[Title/Abstract]) OR patient guid*[Title/Abstract]) OR counsel*[Title/Abstract]	2,264,775
#11	("adherence"[Title/Abstract]) OR "concordance"[Title/Abstract]) OR "compliance"[Title/Abstract]) OR "clinical	339,739
#12	#4 AND #6 AND #10	52
#13	#4 AND #7 AND #10	54
#14	#4 AND #8 AND #10	4
#15	#4 AND #9 AND #10	1052
#16	#4 AND #6 AND #11	29
#17	#4 AND #7 AND #11	23
#18	#4 AND #8 AND #11	1

#19	#4 AND #9 AND #11	578
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Table 4-2: EMBASE Literature Search Strategy

EMBASE Literature Search Strategy		
#1	warfarin:ab,ti OR coumarin:ab,ti	52,100
#2	'anticoagulant agent':ab,ti	408
#3	apixaban:ab,ti OR dabigatran:ab,ti OR rivaroxaban:ab,ti OR edoxaban:ab,ti	17,906
#4	#1 OR #2 OR #3	63,890
#5	#2 OR #3	99,143
#6	knowledge:ab,ti OR education:ab,ti OR understand*:ab,ti OR counseling:ab,ti OR 'patient guidance':ab,ti	2,754,393
#7	'clinical outcome':ab,ti OR 'patient compliance':ab,ti	134,152
#8	smartphone:ab,ti OR 'mobile phone':ab,ti OR 'mobile application':ab,ti	22,060
#9	technology:ab,ti OR 'electronic devic':ab,ti OR 'online system':ab,ti OR telehealth:ab,ti OR 'mobile health application':ab,ti OR internet:ab,ti	502,904
#10	4 AND 6	4,104
#11	4 AND 7	500
#12	4 AND 6 AND 7	43
#13	8 AND 12	1
#14	9 AND 13	1
#15	4 AND 6 AND 8 AND 9	2
#16	4 AND 6 AND 8	6

4.2.3. Data Collection and Selection of Studies

All identified references for inclusion based on the inclusion criteria were imported and sorted using Covidence software. Duplicated references were discarded automatically. The publications were then screened on the basis of their titles, abstracts, and full texts where necessary. They were assessed for eligibility and irrelevant studies were discarded.

4.2.3.1. Data Extraction and Quality Assessment

Data extraction was conducted using Microsoft Excel Version 16.47, and focused on four domains:

1. Characteristics of the study
2. Patient demographics
3. Details about the intervention
4. Study findings

4. Electronic Education Literature Review

Additional information related to the publication (authors, title, year, funding, and conflicts of interest) was also collected to assess study quality.

4.2.3.2. Assessment of Risk of Bias in Included Studies

The risk of bias of the included studies was determined using Cochrane's Tool for assessing risk of bias in randomised trials. [168] This tool provides a framework for assessing the risk of bias in a single result from any type of randomised trial against seven domains:

1. Random sequence generation (selection bias)
2. Allocation concealment (selection bias)
3. Blinding of participants and personnel (performance bias)
4. Blinding of outcome assessment (detection bias)
5. Incomplete outcome data (attrition bias)
6. Selective reporting (reporting bias)
7. Other sources of bias.

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

4.3. RESULTS

4.3.1. Study Selection

Through the database searches, 1,802 records were retrieved, and 1,618 records were screened after de-duplication. Of these, 1,598 studies did not meet the inclusion criteria, and were excluded. Following assessment of the remaining 20 records in full text, 15 were excluded. Reasons for exclusion can be found in Figure 4.1: PRISMA Study Flow Diagram. Five studies were included.

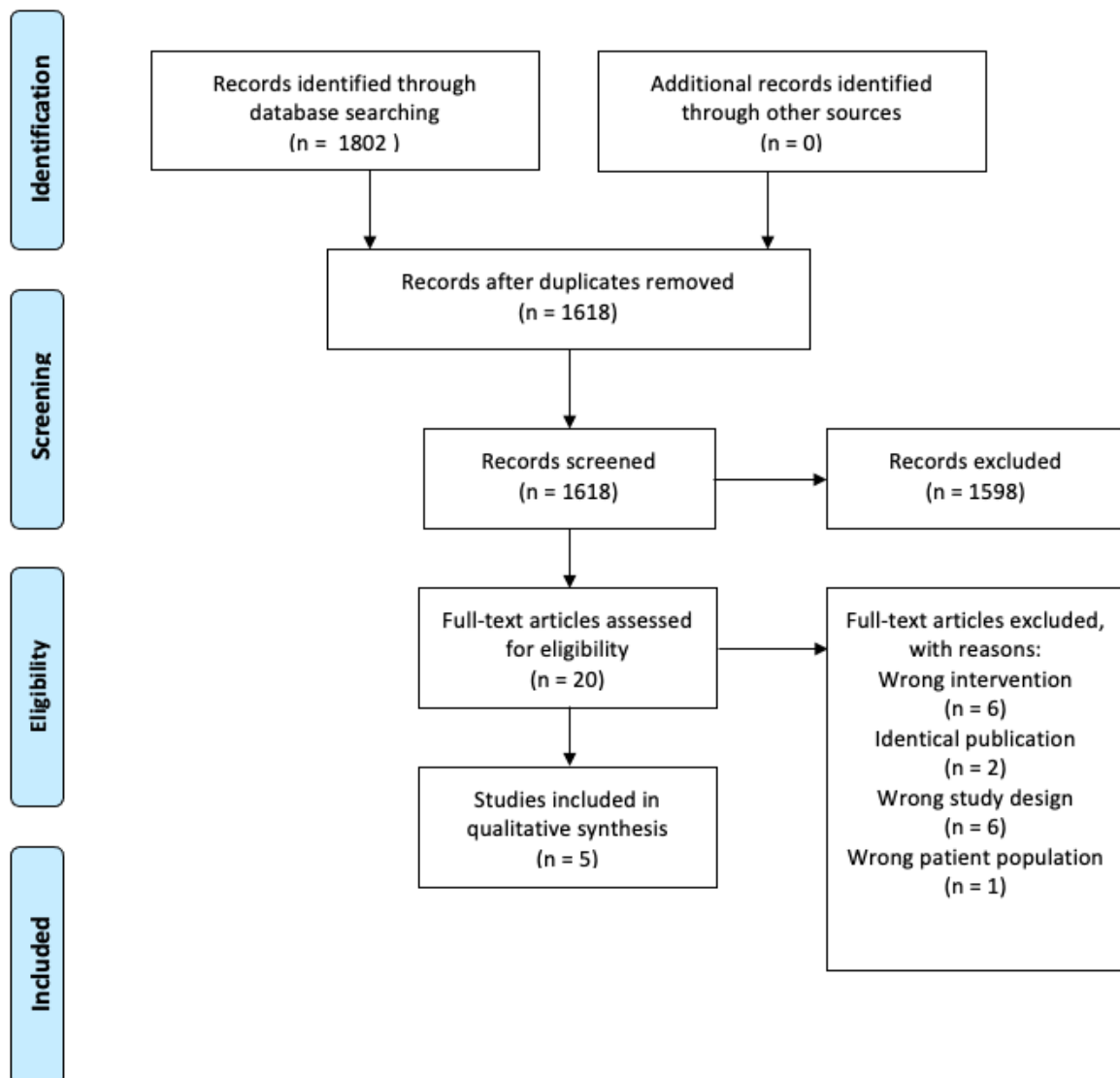


Figure 4.1: PRISMA Study Flow Diagram

4.3.1.1. Included Studies

Five studies have been included (Clarkesmith *et al.*, Moore *et al.*, Guo *et al.*, Talboom-Kamp *et al.*, and Toscos *et al.*). [7-11] Clarkesmith *et al.* is a RCT. [7] Moore *et al.* is a prospective, randomised,

open, parallel-group study. [8] Guo *et al.* is a cluster randomised design pilot study. [9] Talboom-Kamp *et al.* is a parallel cohort design. [10] Toscos *et al.* is a RCT with parallel groups. [11]

These trials compared education of patients using group sessions showing an educational DVD (Clarke-Smith *et al.*), informational video recordings (Moore *et al.*), mobile AF App (Guo *et al.*), self-management plus education (e-learning and group training) to usual care (Talboom-Kamp *et al.*), and patient portal MyChart (Toscos *et al.*), with follow up ranging from seven days after the intervention to 24 months in the five trials. [7-11]

Participants were recruited from various outpatient clinics (Clarke-Smith *et al.*, Talboom-Kamp *et al.*, Toscos *et al.*), in an academic medical centre (Moore *et al.*), and in two hospitals (Guo *et al.*). The number of participants recruited during the trials varied from 40 to 247 in total. [7-11]

Only one of the studies considered patients to be eligible if they were warfarin-naïve (Clarke-Smith *et al.*) [7] Moore *et al.* had a mixture of both warfarin-naïve and those who had previously taken warfarin. [8] Talboom-Kamp *et al.* did not specify whether patients were new to OAC treatment or not, but considering those recruited had already been attending the outpatient service, it can be assumed that participants were previously on OAC therapy. [10] Guo *et al.* recruited participants who had been diagnosed with AF, and didn't specify if all participants were on OAC therapy. [9] Finally, Toscos *et al.* recruited NVAf patients on OACs (DOACs and VKAs), ensuring an even distribution of participants taking DOACs (except for dabigatran, as the trial used an electronic pill bottle which didn't comply with the storage recommendation for this DOAC). [11]

4.3.1.2. Study Interventions

The TREAT intervention by Clarke-Smith *et al.* involved patients attending a group session (consisting of 1-6 patients) for a duration of 1 hour. [7] During the session patients were shown a DVD containing 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. Questions were encouraged and patients completed a worksheet after each 10 minute DVD session. [7]

Moore *et al.* trialled anticoagulation education via a pre-recorded video provided on a tablet device. The video was watched once by participants in the intervention arm. [8]

Guo *et al.* designed the mAF App to incorporate details such as patients' personal health record, stroke and bleeding risk assessments, and a clinical score to aid warfarin control predication,

patient education programmes, patient involvement self-care items, and structured follow-up components. [9]

Talboom-Kamp *et al.* had two intervention groups, both consisting of a training programme in combination with the use of an online self-management portal called Portavita. Group 1 patients used e-learning, group 2 used group training, and group 3 used basic training and acted as the control. [10]

Toscas *et al.* created an algorithm to deliver tailored educational messages via a patient portal named MyChart. Participants in the intervention group of the study were sent educational messages and reminders via this portal throughout the 6-month trial. [11]

4.3.2. Risk of Bias in Included Studies

According to the Cochrane risk of bias tool, the risk of bias of the included studies were assessed and judged 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 4-3, Table 4-4, Table 4-5, Table 4-6 and Table 4-7.

4.3.2.1. Random Sequence Generation (Selection Bias)

Two of the studies randomly allocated the participants using adequate random sequence generation (Clarksmith *et al.*, Moore *et al.*). [7, 8] Therefore, they were deemed as low risk. Two studies were judged as high risk as the randomisation was by unsuitable methods (Guo *et al.*, Talboom-Kamp *et al.*). [9, 10] One of the studies was considered to have an unclear risk of allocation as authors state that group allocation was randomised, but did not outline how (Toscas *et al.*). [11]

4.3.2.2. Allocation Concealment (Selection Bias)

Similarly, two studies were considered as low risk for allocation concealment, because the researcher involved in patient allocation was not otherwise involved in the study (Clarksmith *et al.*, Moore *et al.*). [7, 8] Talboom-Kamp *et al.* allowed patients to choose whether they would be in the intervention or control group, and only randomised which intervention would be given. This study was therefore deemed as high risk. [10] Guo *et al.* was also considered high risk for allocation concealment, as the trial had a cluster randomised design, and the researchers did not state if an independent researcher was involved in allocation. [9] Finally, Toscas *et al.* was also believed to be high risk. Both clinical staff and research team members were involved in the identification of eligible participants. Group assignment was stated to be randomised but the process was not clearly defined. [11]

4.3.2.3. *Blinding (Performance and Detection Bias)*

Blinding of participants was unexpected due to the nature of the interventions. Three of the studies (Moore *et al.*, Talboom-Kamp *et al.*, and Toscos *et al.*) were deemed as high risk due to the authors stating that study participants could not be blinded. [8, 10, 11] The risk for Clarkesmith *et al.* and Guo *et al.* was deemed as unclear, as insufficient information was provided regarding blinding. [7, 9]

With regards to the blinding of outcome assessment, Clarkesmith *et al.* was deemed low risk as a separate researcher was assigned to randomisation of patient data and checking the completeness of follow-up questionnaires. [7] Similarly, in Moore *et al.* no investigators involved in the conduct of the study had access to the schedule during the study, so the study was assessed to be low risk. [8] Talboom-Kamp *et al.* was considered high risk, as personnel were not blinded, therefore detection bias is possible. [10] Guo *et al.* was considered as having an unclear risk, as authors do not mention blinding of participants or personnel during the study [9]. Toscos *et al.* did not blind participants or personnel. The research paper does not mention any separate investigator to conduct data analysis or detection of outcomes, therefore considered as high risk. [11]

4.3.2.4. *Incomplete Outcome Data (Attrition Bias)*

Four studies were considered to have a high risk of attrition bias, as more participants were lost due to follow up in the intervention arms than the control arms. [7, 9-11] Moore *et al.* was considered low risk, with relatively low numbers of participants lost during the study. [8]

4.3.2.5. *Selective Reporting (Reporting Bias)*

A separate protocol was not available for three studies: Moore *et al.*, Guo *et al.*, and Toscos *et al.*. [8, 9, 11] The protocol of the study was instead reported within the results, as part of the methods and study objectives, and these studies were treated as having a high risk of bias. Alternatively, two studies were regarded as low risk of reporting bias as both had published the protocol separately. All outcomes included in the protocols were reported appropriately in the study outcomes. Cost-analysis of both studies had yet to be published. [7, 10]

Table 4-3: Risk of bias for Clarkesmith et al. [7]

Bias	Judgment	Support for Judgement
Random Sequence Generation (Selection Bias)	Low risk	“Computer-generated randomised allocation to intervention or control. “A computer generated list stratified by (a) age (<70 and ≥70 years)/sex and (b) 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, in addition to ‘usual care’.”
Allocation Concealment (Selection Bias)	Low risk	“The randomisation schedule was designed by an independent trials unit and 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.”
Blinding of Participants (Performance Bias)	Unclear risk	Due to the nature of the intervention, patients could not be blind to receiving the educational video. However, it is unclear if the patients were aware if they were in the intervention group.
Blinding of Outcome Assessment (Detection Bias)	Low risk	“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.”
Incomplete Outcome Data (Attrition Bias)	High risk	The initial number of participants (n=46) in the intervention group was reduced to 43 within one month. A further one participant discontinued the study and (n=4) did not return follow up questionnaires. The usual care (n=51, increased to n=54) group had one participant discontinue the study.
Selective Reporting (Reporting Bias)	Low risk	The protocol is made available and all outcomes were reported aside from the cost-effectiveness analysis.
Other Bias	Low risk	No further concerns.

Table 4-4: Risk of bias for Moore et al. [8]

Bias	Judgement	Support for Judgement
Random Sequence Generation (Selection Bias)	Low risk	"Study participants were randomized to 1 of 2 comparator arms: informational video recordings (intervention) or face-to-face oral counselling (control). A concealed-variable permuted blocks randomization scheme (blocks of 8, 6, 4, or 2) was used to maintain counsellor blinding until the participant was formally enrolled."
Allocation Concealment (Selection Bias)	Low risk	"A coinvestigator who was not involved in the conduct of the study (JHH) generated the randomization schedule: SAS Proc Plan, version 9.2 (SAS Inc, Cary, NC)... No investigators involved in the conduct of the study had access to the schedule until study interventions, measurements, and analyses were completed."
Blinding of Participants (Performance Bias)	High risk	"Because the study intervention could not be blinded."
Blinding of Outcome Assessment (Detection Bias)	Low risk	"No investigators involved in the conduct of the study had access to the schedule until study interventions, measurements, and analyses were completed."
Incomplete Outcome Data (Attrition Bias)	Low risk	"One participant in the video group was not included in the primary end point analysis because of missing socioeconomic status. OAK test scores were missing for 2 participants at baseline."
Selective Reporting (Reporting Bias)	High risk	The protocol is not available for this study.
Other Bias	High risk	"Although it was powered to compare the total time required for video versus face-to-face counselling, we did not anticipate differences based on prior warfarin use. As a result, this limited our general conclusions and necessitated that we compare the 2 counselling methods within warfarin-use strata, thereby reducing the power of each individual comparison. Another unanticipated limitation of our study was the difficulty we encountered in recruiting warfarin-naïve participants."

Table 4-5: Risk of bias for Guo et al. [9]

Bias	Judgement	Support for Judgement
Random Sequence Generation (Selection Bias)	High risk	"Patients with atrial fibrillation were randomized to 2 groups (mAF App vs usual care) in a cluster randomized design. This was a clustered randomized study, and a selection bias could exist."
Allocation Concealment (Selection Bias)	High risk	As above, and study had no information on whether an independent researcher was involved in the allocation process.
Blinding of Participants (Performance Bias)	Unclear risk	Insufficient information provided regarding the blinding of participants.
Blinding of Outcome Assessment (Detection Bias)	Unclear risk	No mention of blinding of participants or personnel during study.
Incomplete Outcome Data (Attrition Bias)	High risk	The intervention group began at n=113 and had n=71 after 3 months. The control group lost no participants during the 3 month follow up period.
Selective Reporting (Reporting Bias)	High risk	The protocol is not available for this study.
Other Bias	High risk	"The clinician's preference for oral anticoagulants may have contributed to a higher rate of non-vitamin K antagonist oral anticoagulant use in the mAF App group. The educational program could have made the patients more aware and thus be more likely to receive non-vitamin K antagonist oral anticoagulants."

Table 4-6: Risk of bias for Talboom-Kamp et al. [10]

Bias	Judgement	Support for Judgement
Random Sequence Generation (Selection Bias)	High risk	"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." "Patients who did not wish to start with self-management were invited to participate in a parallel cohort group receiving usual care (group 3)."
Allocation Concealment (Selection Bias)	High risk	"Patients were free to volunteer, bias might have occurred in our study groups." Allocation concealment was not conducted as participants had the choice of which group to participate in – intervention or control.
Blinding of Participants (Performance Bias)	High risk	Participants were not blinded as they chose whether they would be in the intervention or control group. No report of blinding researchers.
Blinding of Outcome Assessment (Detection Bias)	High risk	The subjective outcome results could have been subject to bias as no blinding was done.
Incomplete Outcome Data (Attrition Bias)	High risk	"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."
Selective Reporting (Reporting Bias)	Low risk	The protocol is available separate to the study and all outcomes are reported on, except for a cost analysis.
Other Bias	High risk	"A 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."

Table 4-7: Risk of bias for Toscos et al. [11]

Bias	Judgement	Support for Judgement
Random Sequence Generation (Selection Bias)	Unclear risk	"Group assignment was randomised but not blinded." Methods of randomisation was not mentioned in the study.
Allocation Concealment (Selection Bias)	High risk	Staff and research team members were involved in the identification of participants, with the process of randomisation not clearly defined.
Blinding of Participants (Performance Bias)	High risk	"Group assignment was randomised but not blinded."
Blinding of Outcome Assessment (Detection Bias)	High risk	No blinding of participants or personnel – detection bias is possible.
Incomplete Outcome Data (Attrition Bias)	High risk	N=2 participants were lost to follow-up, n=2 were withdrawn, and n=4 were excluded from analysis in the intervention arm. N=1 was withdrawn, n=2 died, n=1 was excluded from analysis in the control arm.
Selective Reporting (Reporting Bias)	High risk	No separate protocol has been made available for the study, and has been included in the methods of the study.
Other Bias	High risk	"Our outcomes and participant demographics suggest the presence of a potential volunteer bias and/or ceiling effect. Both the intervention and control groups demonstrated much higher OAC adherence rates than what is reported among AF patient samples." "The study sample was overwhelmingly white...and educated... limiting generalisability." "Our sample also likely had higher health engagement and technological familiarity than the average AF patient, as patients without computer or Internet access and those who did not have or were unwilling to create a MyChart® account were not included in this study."

4.3.3. Effects of Interventions

4.3.3.1. Patients' Knowledge and Comprehension

Clarkesmith *et al.*, Moore *et al.*, Guo *et al.*, and Toscos *et al.* reported on patients' knowledge levels throughout the studies using different means of measurement. [7-9, 11]

Clarkesmith *et al.* reported significant improvement in patients' knowledge scores over time, but this difference was not seen between groups. Both groups had good knowledge levels at baseline. Knowledge scores weakly predicted TTR at the six month follow-up, but this was not seen at any other timepoint. [7] Moore *et al.* saw that there was no difference in knowledge scores of participants post-counselling between the different counselling methods. Prior warfarin use was not significantly associated with differences in overall knowledge scores when comparing the two counselling scores, nor was there evidence of an interaction. However, there were poor follow-up rates reported for the knowledge test on day 7, with 8 intervention participants and 10 control participants completing the assessment. [8] Guo *et al.* observed a significant increase in patients' knowledge in those using the mAF App over time, which was not seen in the usual care group. [9] Toscos *et al.* saw that the intervention group demonstrated higher levels of knowledge at study completion than the control group when knowledge levels were controlled at baseline. [11]

4.3.3.2. Time in Therapeutic Range (TTR)

Clarkesmith *et al.* and Talboom-Kamp *et al.* reported on the impact of the interventions on participants' TTR values. [7, 10]

The intervention group of Clarkesmith *et al.* spent significantly more time in therapeutic INR range during the initial six months of OAC initiation than the control group. These differences were consistent at the 12 month follow-up, but were not significant. [7] The Talboom-Kamp *et al.* study reported no significant differences in TTR values over time, between the groups, or between the groups over time. [10]

4.3.3.3. Quality of Life (QoL)

Clarkesmith *et al.*, Talboom-Kamp *et al.*, Guo *et al.* included QoL measurements in their studies. [7, 9, 10]

Clarkesmith *et al.* measured QoL using the Atrial Fibrillation QoL questionnaire, whereas Talboom-Kamp *et al.* used the EuroQol-5d (EQ-5D) questionnaire. [7, 10] Guo *et al.* measured QoL using the EuroQol questionnaire. [9]

Participants in the intervention group had lower baseline QoL subscale than usual care group in the TREAT trial. These values increased at one month follow-up and at all subsequent follow-ups there were no significant differences in QoL scores between groups. [7] The PORTALS study only reported QoL at baseline but no significant differences were found between the three groups. [10] The mAF App study reported that QoL scores significantly improved in the mAF arm compared with usual care at baseline, 1-month, and 3-months. [9]

4.3.3.4. Change in Psychological Measures and Illness Perceptions

Clarkesmith *et al.* assessed psychological measures in participants from baseline, 6 months and 12 months during the study. There were no significant changes in any variable between groups at 6 or 12 months. Participants' perception of AF's timeline (e.g. acute/chronic/cyclical) significantly changed over time, but no differences existed between groups. Patients' perceived treatment control, emotional representation, and illness coherence scores also changed significantly over time, but not between groups. [7]

4.3.3.5. Mean Total Counselling Time

Moore *et al.* used average counselling time as their primary endpoint. The values greatly reduced in the video group. However, prior warfarin use was significant, and a noteworthy interaction between prior warfarin use and counselling method was observed. As a result, comparisons were made between the two groups (warfarin-naïve and restart patients). This showed a mean time in restart participants reduced by 8.71 minutes when compared to face-to-face counselling group ($p < 0.001$). The mean time in new start participants receiving the video was reduced by 2.31 minutes, which was not statistically significant. [8]

4.3.3.6. Platform Usage

Talboom-Kamp *et al.* reported no significant difference between platform usage of group 1 and 2 during three time periods over 6 months. [10]

4.3.3.7. Medication Adherence

Guo *et al.* saw that drug adherence (measured using the 3-item Adherence Estimator Scores) was significantly improved with the mAF App at months 1 and 3 compared to patients in usual care. Patients with the mAF App were more likely to receive a DOAC versus those with usual care. [9]

Toscos *et al.* measured medication adherence using AdhereTech's Wireless Smart Pill Bottle. The intervention and control groups in the study showed adherence rates of 93.1% and 89.5%,

respectively. In the main effects-only model, the intervention had a slightly significant impact on adherence ($p=0.08$). The moderated effects of intervention by age demonstrates that younger participants benefitted more from the intervention in terms of adherence. The type of medication also moderated the effect – participants taking rivaroxaban had significantly higher adherence in the intervention group versus the control group. [11]

4.3.3.8. Severe Complications or Adverse Events

Clarkesmith *et al.*, Talboom-Kamp *et al.*, and Toscos *et al.* included data on adverse events. [7, 10, 11]

A total of 8 adverse events occurred during a 12-month period of the TREAT study, seven of which were in the usual care group (including ischaemic non-fatal strokes, major and minor bleeding episodes, and a non-cardiac related death). One event occurred in the intervention group and was a peripheral embolism. [7] Talboom-Kamp *et al.* reported three severe complications over the 18-month trial: two muscular bleedings in the e-learning group and one cerebrovascular accident among patients receiving group training. No adverse events were reported in the control group. [10] Although Toscos *et al.* state that patients ($n=2$) had withdrawn from the study due to illness, they do not specify if the illness was cardiac-related or if any specific adverse events occurred. [11]

4.4. DISCUSSION

4.4.1. Primary Endpoints of the Studies

It is clear that each intervention had varying levels of influence over the study outcome. Table 4-8 provides an overall summary of the study interventions, intervention and control arms, and a brief summary of the primary outcomes. The choice of primary outcome ranged from time spent counselling, to time in therapeutic control, to participants' knowledge. [7-11] Endpoint(s) are specific measures of trial outcome(s), and should address the trial objective(s). Primary endpoints are usually measures of efficacy which tackle the main research question. [169]

Moore *et al.*'s study focused on the efficiency of video-based education, therefore the choice of total time spent counselling as the primary endpoint directly relates to the study's aims. Mean total time in counselling significantly reduced in the video arm, but participants previously on warfarin saw a more significant reduction in this compared to those new to warfarin. [8]

Two of the studies chose TTR as the primary outcome. Both of these recruited warfarin-only participants. TTR is a helpful marker, and shows the percentage of time patients' INR was within the target range. Patients with elevated TTR levels are reported to have better outcomes such as

reduced stroke, major bleeding events and death. [170] Talboom-Kamp *et al.* found no significant differences in TTR between the groups. [10] The intervention participants in Clarkesmith *et al.* had significantly better control over their INR levels for the first 6 months of the study. This difference was sustained at 12 months but was not significant. [7]

Knowledge assessment was used as the primary outcome of both Guo *et al.* and Toscos *et al.*. [9, 11] Patient knowledge about AF and its management is often limited, especially around initial diagnosis where the majority of treatment decisions are discussed and made. [171] Toscos *et al.* reported significant differences in the AF knowledge levels of the intervention group with the digital health technologies at study completion versus control. [11] Guo *et al.* reported significant improvements in the knowledge levels of the intervention group over time with the mAF App, which was not reflected in the control group. [9]

Without a similar comparable measurement used in each study to monitor the effect of each intervention, it is challenging to compare the effect of each educational instrument.

4.4.2. Quality of the Studies

RCTs represent the gold standard for generating evidence. RCTs are the least biased way of measuring and comparing treatment effects. [172] Parallel-group design is the most commonly used study design. This is where participants will be randomised to one or more study arms and each arm will be allocated a different intervention. [173]

Cluster randomised studies involve the randomisation of groups or clusters of individuals, rather than the individuals themselves. Such trial design is prone to selection bias, as it is not always possible to conceal treatment allocation. [174] Guo *et al.* used this design and acknowledged the potential for bias. However, the authors stated that the distribution of comorbidities between mAF App and usual care arms were not significantly different. [9]

Talboom-Kamp *et al.* employed a parallel cohort design, allowing participants to select intervention or control. The only randomisation used in the study was for which intervention the patients received. [10]

The sample size for all included studies were relatively small, with a total of 624 participants recruited overall. Thus, these trials are more likely to be insufficiently powered to detect clinically and statistically significant differences between groups. [175] Each study used a different method to calculate sample size and the actual sample size attained was in line with the calculation. The sample size chosen by Clarkesmith *et al.* for the primary endpoint was based on the ACTIVE-W

cohort by Connolly *et al.*. [176] A sample size of 156 participants in two groups of 78 was therefore required, allowing for a 20% attrition rate. [7] Moore *et al.* calculated their sample size of 38 participants in two groups of 19, for a study power of 85% and a 2-sided α of 0.05. [8] Guo *et al.* used a sample size calculation with a 20% attrition rate with at least 80% power to detect an 18.5% increase in knowledge between baseline and follow-up. This gave a total of 112 patients in two groups of 56, with an α of 0.05. [9] Talboom-Kamp *et al.* aimed to detect the effect of their intervention at a power of 80% and an α of 0.05, calculating a sample size of 189 in total with 63 patients per arm. [10] Finally, Toscos *et al.* set a recruitment target of 160 in total with 80 patients per group, based on a power calculated of 80% an α of 0.05. [11]

The risk of bias assessment showed a potential for a high risk of bias in each of the studies, particularly Toscos *et al.*, Talboom-Kamp *et al.*, and Guo *et al.*. [9-11]

Moore *et al.* and Clarkesmith *et al.* provided information about the random sequence generation when assigning patients to the various study arms, therefore they were deemed a low risk of selection bias. [7, 8] Toscos *et al.* stated that group assignment was randomised but provided no details of the method used, therefore they had an unclear risk. [11] Guo *et al.* and Talboom-Kamp *et al.* were at high risk of selection bias due to the methods of randomisation used. [9, 10]

The majority of the studies were at a high risk of performance bias. Due to the nature of the intervention, blinding of the participants was not always possible. Therefore, Moore *et al.*, Talboom-Kamp *et al.*, and Toscos *et al.* were deemed as high risk as authors stated participants were not blinded. [8, 10, 11] Both Clarkesmith *et al.* and Guo *et al.* had an unclear risk of performance bias due to insufficient detail provided by the authors. [7, 9]

Two of the studies (Clarkesmith *et al.* and Moore *et al.*) were deemed at low risk of detection bias, one study by Guo *et al.* had an unclear risk due to insufficient detail, and both Toscos *et al.* and Talboom-Kamp *et al.* were considered high risk of detection bias due to inadequate blinding. [7-11] Risk of attrition bias was deemed as high with four of the studies: Toscos *et al.*, Talboom-Kamp *et al.*, Guo *et al.*, and Clarkesmith *et al.*. [7, 9-11] As regards reporting bias, only two of the studies (Clarkesmith *et al.* and Talboom-Kamp *et al.*) had published separate protocols, and therefore were considered low risk. [7, 10] The other three studies (Moore *et al.*, Guo *et al.*, and Toscos *et al.*) were deemed as high risk as the protocol was reported within the study itself. [7-11]

4.4.3. Types of Participants

It would be interesting to consider which patients were OAC-naïve and which had a history of taking the OAC within each study. Clarkesmith *et al.* had only recruited patients new to warfarin. [7] Moore *et al.* had a mixture of both, and compared the results between both groups. [8] Talboom-Kamp *et al.* recruited patients already signed up to their outpatient service, so it is expected that these participants had already been taking OACs. [10] Guo *et al.*'s participants had been previously diagnosed with AF, but it is unclear if all participants were taking OACs. [9] Toscos *et al.* included patients with NVAf taking DOACs. [11] The breakdown of results of interventions based on whether patients were new to their diagnosis/treatment could be helpful to consider. As seen in Moore *et al.*, the prior use of warfarin was a significant factor in the mean total counselling time. This means that the use of educational videos in this study significantly reduced pharmacist time required for counselling, but this benefit was primarily seen in patients with prior warfarin use. [8] Future studies should look to evaluate the differences seen between those new to the therapy and those with a history of treatment.

4.4.4. Limitations of the Review

Like any study, this review was subject to intrinsic limitations. As reviews can only include what is found by the searches, there is an element of publication bias present. Further studies are required to support the evidence and fully determine the impact of the interventions on clinical outcomes. This review was limited to trials reported in the English language, which could have excluded relevant non-English language studies.

Table 4-8: Summary of Included Studies

Study	Intervention	Intervention Group	Control Group	Primary Endpoint
Clarksmith <i>et al.</i> [7]	TREAT Intervention	One group session (between 1-6 patients) for one hour, during which the patients were shown a DVD containing information about the OAC	Standard yellow booklet including information on OAC	The intervention group spent significantly more time in therapeutic INR range during the first 6 months
Moore <i>et al.</i> [177]	Video shown on a tablet device	Video-based counselling	Face-to-face counselling	Mean total counselling time was significantly reduced in the video group
Guo <i>et al.</i> [9]	Mobile AF app	mAF App including personal health record, stroke and bleeding assessment, patient educational programmes, patient involvement self-care items, and structured follow-up components	Usual care, not specified	Significant improvement in knowledge in intervention group over time, this was not observed in control group
Talboom-Kamp <i>et al.</i> [10]	Online self-management portal	1. E-learning PORTALS group 2. Face-to-face group training	3. Basic short training, usual care	No differences were found in therapeutic control between the 3 groups
Toscos <i>et al.</i> [11]	Three digital health technologies: a patient portal, an electronic data feed, and a smart pill bottle	The content of the educational messaging, nudges and cadence were tailored based on results from user-centred design studies and delivered via the MyChart patient portal	Standard care, with paper based surveys at end of trial	The intervention group demonstrated higher AF knowledge at study completion than control group and more portal logins throughout the trial

4.5. CONCLUSION

Although the findings in the studies were generally positive and suggest benefits for the use of electronic education on OAC patients, their limitations (such as small sample sizes and high risk of bias) mean that recommendations for practice cannot be made based on this review and further research is required. Ideally, larger sample sizes should be recruited to future studies to increase the power of the findings. Researchers might consider including information on whether patients are new to the treatment or not, as recommended by Moore *et al.* based on their results. [8] The tools used to assess results should be standardised to aid comparison across similar research with pooled outcomes. As acknowledged by Toscos *et al.*, clinical outcomes such as hospitalisation rates and thromboembolic events are an important consideration when evaluating the impact of interventions of this kind, and future research should investigate this to build upon initial research. [11]

5. Quality of Counselling Resources for Direct Oral Anticoagulants

5.1. INTRODUCTION & BACKGROUND

As discussed throughout this thesis, adherence is essential for DOAC patients to ensure the safety and effectiveness of the drug. [33] Patients and HCPs alike should consider even a single missed dose as serious, as DOACs have a fast offset of action, meaning patients can become coagulated quickly. This leads to an increased risk of stroke or another thromboembolic event. [3, 59] Studies have found that poor adherence with OACs is also linked to increased mortality rates for patients. [178, 179] One study found that DOAC patients do not consider missing a dose as serious an issue as those taking warfarin. [3] Several studies have shown high percentages of DOAC patients with poor adherence rates. [180-182]

Research has found that these issues could be explained by DOAC patients' limited contact with HCPs, due to the reduced need for monitoring compared with warfarin. [183-188] The high cost of DOACs and potential gastrointestinal side effects seen with dabigatran may play a role in the pattern of poor adherence with these drugs. [189] It is seen that patients switching from warfarin to DOAC therapy have improved adherence compared to those starting a DOAC who were anticoagulant naive, which may indicate that warfarin patients had received better education on the importance of adherence. [178] Adherence has also been shown to worsen over time, highlighting a need for continuous patient education. [179, 183-193]

The EHRA has acknowledged the need for improved patient education on DOACs. [13] It has been shown that pharmacist counselling interventions can significantly improve outcomes as regards bleeding incidence, hospital readmissions and adherence. [194-200] Educational needs of DOAC patients identified include basic knowledge of their condition, treatment, the importance of adherence, awareness of what to do if an adverse event occurs, and ability to differentiate between minor and major events. [201] Patients also have a responsibility to take a proactive role in their own treatment as well as being empowered to do so by their HCPs.

Whilst the number of resources available to patients and HCPs continues to grow, it is necessary to consider the quality of the materials used. The NALA in Ireland advocates for the production of documents that consider those with low literacy levels. [202] NALA defines literacy as listening and speaking, reading, writing, numeracy and using everyday technology to communicate and handle

information. [203] Health literacy refers to accessing, using and understanding information to make health decisions. [204] International research has shown that people who are more informed about their health have better consultations with their HCPs, are more knowledgeable about their medicines, and are more likely to be compliant with their medication. This results in improved health outcomes for these patients. [78]

A recent study evaluated web-based education materials for patients taking DOACs for their actionability and understandability. [205] The researchers used the Patient Education Materials Assessment Tool (PEMAT) which revealed that the majority of the materials included were highly understandable but poorly actionable. [206] It was noted that most did not provide a summary of key points or visual aids for understandability, nor did they include tangible tools, such as checklists to prompt user action.

Readability is defined via several formulas based on sentence length, word familiarity, syllables, and other factors through scores which relate to a grade level needed to understand the presented information. [207] It is an effective measure to ensure literature is easy to comprehend. It is important to evaluate the content of educational materials for DOACs based on their readability and quality, considering current available guidelines supported by the relevant governing health bodies. [12, 72]

5.2. AIMS AND OBJECTIVES

5.2.1. Aims:

The aim of this study was to assess the quality and readability of counselling resources for DOACs.

5.2.2. Objectives:

To identify the counselling resources available to both patients and pharmacists regarding DOACs.

1. To evaluate the content of available resources by auditing them against:

- EHRA guidelines; [13]
- iPACT guidelines. [72]

2. To assess the readability of currently available resources through determination of:

- Cosgrove's readability checklist; [208]
- Flesch reading ease scores; and
- Flesh-Kincaid grade level. [209]

3. To highlight the significant points upon which a pharmacist should counsel a patient taking DOACs.

5.3. METHODS

5.3.1. Ethics Approval

As this study did not have research participants and was based on information in the public domain, research ethics approval was not required.

5.3.2. Identification of Resources

This study was limited to investigation of English language resources and the search strategy therefore focused on material from countries with English-speaking majorities with a population > 4 million. [210] Resources were identified: (a) through targeted searches of the manufacturers' websites for the four licensed DOACs, and the websites of cardiovascular patient support organizations and government health agencies in the relevant countries; (b) through structured internet searches combining terms for the anticoagulants of interest (rivaroxaban, dabigatran, edoxaban, apixaban, DOAC, NOAC, oral anticoagulant) with phrases describing the type of information sought (patient information, patient counselling, patient advice, patient leaflet).

Google was used for the latter search component, as it is the most widely used search engine (74% of desktop searches and 93% of mobile searches) and the search was limited to the first two pages of results from each search, in order to replicate the likely search strategy of a patient or pharmacist seeking an information resource online. [211, 212] While 'oral anticoagulant' was used to help identify material that included advice on DOACs alongside warfarin and did not mention the individual drugs by name, the search was limited to the years since 2010 (first DOAC authorization date) to reduce the number of results relating to warfarin only. Only freely accessible online resources were considered, to reflect those readily available to patients and practitioners. Eligible materials included both website-based and downloadable resources, either targeted directly at patients or designed to support healthcare practitioners in providing advice to patients.

5.3.3. Content Evaluation

In the absence of a single, definitive audit standard for this topic, the content of the resources was evaluated against the recommendations of two leading international bodies: the EHRA and the iPACT. [13, 72]

5.3.4. Readability

For resources targeted directly at patients, the Flesch Reading Ease and Flesch-Kincaid Grade Level scores were determined using Microsoft Word 365 (Microsoft Corporation, Washington, USA). For additional parameters affecting readability such as presentation and format, resources were evaluated against Cosgrove's readability checklist. [208] This tool is derived from guidance co-developed by Ireland's Health Information and Quality Authority and National Adult Literacy Agency and an assessment tool prepared by the United States Agency for Healthcare Research and Quality. [213, 214]

5.3.5. Data Analysis

Data was compiled in a Microsoft Excel 365 spreadsheet (Microsoft Corporation, Washington, USA) with standardized headings to ensure consistency of data collection. Data were then coded and imported into IBM SPSS Statistics v. 26 (IBM, New York, USA) for quantitative analysis. Proportions were compared using chi-squared analysis, while central measures were compared using Student's t-test for parametric data and the Kruskal-Wallis H-test for non-parametric comparisons of two and multiple groups respectively, taking $p < 0.05$ as significant.

5.3.6. Counselling Aid for Pharmacists

Based on the data and trends identified, along with the EHRA and iPACT guidelines [13, 72], an *aide memoire* for pharmacists was developed. This standardised information found across many resources, as well as practical information on administration and side effects.

5.4. RESULTS

5.4.1. Overview

In total 66 resources were identified: 32 targeted directly at patients and 34 to support HCPs' patient counselling. 23 were from DOAC manufacturers, with the remainder from government agencies (15), healthcare professional organizations (18) and patient organizations. (10)

5.4.2. Content of Resources

The mean number of EHRA criteria covered across all resources was 5.74 (standard deviation (SD) 2.303) from a maximum of 8. The mean number of iPACT criteria covered was 6.61 (SD 2.648) from a maximum of 10.

Frequencies for adherence of patient and HCP resources to the EHRA criteria are shown in Table 5.1. When comparing patient and HCP resources in terms of adherence to the EHRA criteria overall, it was found that resources designed for patients had a significantly higher mean number of EHRA criteria present (mean + standard deviation: 6.88 + 1.48) compared with those for HCPs (4.68 + 2.45), $p < 0.001$. The criteria where it was most apparent that patient resources were adhering more closely to the EHRA guidelines were "Mechanism of action" ($p=0.022$), "Missed doses/Dosing errors" ($p<0.001$), "Bleeding/Trauma" ($p=0.004$), "Informing a HCP before a procedure" ($p<0.001$) and "When to contact a HCP" ($p<0.001$), with a significantly larger fraction of patient resources mentioning these topics when compared to HCP resources. Overall adherence of resources to the EHRA criteria was also examined, with no single recommended topic being consistently mentioned throughout both patient and HCP resources.

Table 5-2 displays frequencies for adherence of patient and HCP resources to the iPACT criteria. No statistically significant difference was found overall between the mean number of iPACT criteria present in resources designed for patients (mean $\pm$ standard deviation: 6.53 $\pm$ 2.38) compared with those for HCPs (6.68 $\pm$ 2.91), $p = 0.583$. However, it was noted that a significantly higher fraction of patient resources mentioned "How to act in an emergency situation/Patient Alert Card" ($p=0.001$), and "Side effects" ($p=0.022$) when compared to HCP resources. It was also noted that a significantly higher fraction of HCP resources discussed "Duration of therapy" compared to patient resources ($p<0.001$). As with the EHRA criteria, overall adherence of resources to the iPACT criteria was examined, with no single recommended topic being consistently mentioned throughout both patient and HCP resources.

Table 5-1: Audit of resources against European Heart Rhythm Association recommendations - comparison of resources directly for patients and those supporting healthcare professionals' counselling [62]

Recommendations for Inclusion	Number of Resources in Which Present			
	Patient Resources (n=32)	HCP Resources (n=34)	P (Chi-squared test)	Overall (n=66)
Indication	29 (90%)	30 (88%)	0.752	59
Mechanism of Action	29 (90%)	23 (68%)	0.022	52
Missed Doses/Dosing Errors	26 (81%)	14 (41%)	<0.001	40
Bleeding/Trauma	31 (97%)	24 (71%)	0.004	55
Drug Interactions	27 (84%)	29 (85%)	0.917	56
Informing a HCP Before Procedures	26 (81%)	10 (29%)	<0.001	36
When to Contact a HCP	31 (97%)	9 (26%)	<0.001	40
Monitoring	21 (66%)	20 (59%)	0.569	41

Table 5-2: Audit of resources against International Pharmacists Anticoagulation Care Taskforce recommendations - comparison of resources directly for patients and those supporting healthcare professionals' counselling [63]

Recommendations For Inclusion	Number of Resources in Which Present			
	Patient Resources (n=32)	HCP Resources (n=34)	P (Chi-squared test)	Overall (n=66)
Benefits of Treatment	19 (59%)	20 (59%)	0.964	39
Risk of Treatment	21 (66%)	26 (77%)	0.331	47
How to Prevent Complication	10 (31%)	13 (38%)	0.552	23
How to Act in Emergency Situation/Patient Alert Card	23 (72%)	11 (32%)	0.001	34
Reason for Taking DOAC	26 (81%)	25 (74%)	0.454	51
Duration of Therapy	8 (25%)	28 (82%)	<0.001	36
Food Intake	23 (72%)	30 (88%)	0.095	53
Drug Interaction	27 (84%)	30 (88%)	0.648	57
Side Effects	31 (97%)	27 (79%)	0.022	58
Reasons Why Therapy May Be Suspended e.g., Surgery	21 (66%)	17 (50%)	0.199	38

5.4.3. Readability

A summary of readability parameters for patient resources is shown in Table 5-3 and Table 5-4. Results were generally positive, with all 32 resources using simple, personal language and limiting each paragraph to just one idea. Twenty-three resources used readable font, but eight resources

had small font, narrow spacing or excessive text making them more difficult to read. Flesch Reading Ease scores indicate how easily people can understand a piece of text (higher scores being more understandable), and the Flesch-Kincaid grade level represents the US grade level of education required to understand a particular piece of text (lower grade levels being more understandable).

The median Flesch Reading Ease score was 52.6 (interquartile range 12.8). Only three resources scored above 60% on the reading ease scale, with the majority of resources scoring between 51-60%, which is considered slightly difficult to read. There was no statistically significant difference ($p = 0.19$, Kruskal-Wallis H-test) between the reading ease scores for patient materials from different source types (manufacturer, patient organization *etc.*). The median Flesch grade level was 9.9 (interquartile range 2.95). Twenty-nine of the thirty-two resources had a grade level ≥ 8 , with the majority ($n=21$) having a grade of 10 or above. Again, there was no significant difference between the median Flesch-Kincaid grade levels for patient materials from different source types ($p = 0.006$, Kruskal-Wallis H-test).

Table 5-3: Readability of patient resources evaluated against Cosgrove's readability checklist [208]

Readability	Patient Resources (n=32)
Were the resources subject to literary proofing?	3 yes 29 unknowns
Were they translated into different languages?	2
Were abbreviations and acronyms explained?	28
Was simple language used?	32
Was personal language used? (I/we/you)	32
Was each paragraph limited to one idea?	32
Was the font used readable?	23
Contrast between text colour & background?	31
Images used clear and relevant to text?	5
Were visual clues used to draw attention to key points? (Bubbles, boxes)	8

Table 5-4: Readability Scores

	Number of patient resources (n=32)
Flesch Reading Ease Score	
>60%	3
51-60%	18
40-50%	8
<40%	3
Flesch-Kincaid Grade Level	
<8	3
8-9	8
10-11	12
>11	9

5.4.4. Comparison of Manufacturer and Non-Manufacturer Resource Content

A summary of the content of manufacturers' resources versus non-manufacturers' resources can be found in Table 5-5. While variation was observed, the only statistically significant differences were between the proportions of resources advising upon "Missed dose/dosing errors", "Monitoring" and "Reasons why therapy may be suspended, e.g., surgery".

Table 5-5: Comparison of resources produced by drug manufacturers and those from other sources

	Number of resources in which present		
	Manufacturers' Resources (n=23)	Non-manufacturers' Resources (n=43)	P (Chi-squared test)
EHRA Recommendations			
Indication	20 (87%)	39 (91%)	0.643
Mechanism of Action	17 (74%)	35 (81%)	0.483
Missed Doses/Dosing Errors	18 (78%)	22 (51%)	0.032
Bleeding/Trauma	19 (83%)	36 (84%)	0.908
Drug Interactions	19 (83%)	37 (86%)	0.713
Informing a HCP Before Procedures	16 (70%)	20 (47%)	0.073
When to Contact a HCP	16 (70%)	24 (56%)	0.276
Monitoring	10 (44%)	31 (72%)	0.022
IPACT Recommendations			
Benefits of Treatment	14 (61%)	25 (58%)	0.830
Risk of Treatment	18 (78%)	29 (67%)	0.355
How to Prevent Complications	9 (39%)	14 (33%)	0.593
How to Act in an Emergency Situation/Patient Alert Card	13 (57%)	21 (49%)	0.552
Reason for Taking DOAC	20 (87%)	31 (72%)	0.170
Duration of Therapy	9 (39%)	27 (63%)	0.066

	Number of resources in which present		
	<i>Manufacturers' Resources (n=23)</i>	<i>Non-manufacturers' Resources (n=43)</i>	<i>P (Chi-squared test)</i>
Food Intake	19 (83%)	34 (79%)	0.729
Drug Interactions	19 (83%)	38 (88%)	0.522
Side Effects	18 (78%)	40 (93%)	0.088
Reasons Why Therapy May Be Suspended, e.g., Surgery	18 (78%)	20 (47%)	0.013

5.5. DISCUSSION

5.5.1. Main Findings

This study set out to critically examine the quality of counselling resources for DOACs. The results show that there are major differences in the content of resources aimed at HCPs compared to those aimed at patients. Resources for patients included more information on the types of DOACs and how they function compared to HCP resources. One significant finding to emerge from this study was that manufacturer resources for patients had more information on patient counselling points than the non-manufacturer resources. Research into AF patients' education needs, and attitudes has shown knowledge gaps in patients around disease symptoms and medication side effects such as bleeding risk. [215] It is important that educational resources produced are of good quality, are readable, and contain the essential counselling points as detailed in the EHRA and iPACT guidelines. [13, 72]

5.5.2. Comparing Content to the EHRA and iPACT Guidelines

The EHRA guidelines provide recommendations for content of resources for DOACs. [13] The guidelines are comprehensive, including the points HCPs should counsel patients on in detail. Our research shows that resources designed directly for patients had a significantly higher mean number of EHRA criteria present compared to resources aimed at supporting HCPs' counselling. Key areas that patient resources discuss but HCP resources neglect are "Mechanism of action", "Missed doses/Dosing errors", "Informing a HCP before a procedure" and "When to contact a HCP". It is comprehensible that the latter two points are omitted from HCP resources, but they are essential information points for patients. However, significantly more patient resources also mentioned "Bleeding/Trauma" when compared with HCP resources, which is worrying considering that bleeding is the most common adverse event which occurs with DOACs.

Studies exploring awareness and understanding of VTE in patients at risk conclude that baseline knowledge of VTE in patients at risk is extremely low without counselling. [5, 216-219]. Table 5-6

details some of the knowledge gaps surrounding VTE in patients at risk. “Missed doses/Dosing errors” is one such knowledge gap and it is essential that DOAC patients are fully informed on what to do in such a situation, as adherence is key to treatment success.

Table 5-6: Examples of knowledge gaps of VTE in patients at risk [5, 216-219]

- | |
|--|
| <ul style="list-style-type: none"> • Risk factors for VTE e.g., cancer patients being unaware that cancer is a risk factor for VTE • Signs and symptoms of VTE e.g., awareness that swelling of the leg is a symptom of VTE • VTE treatment side effects • Terminology of VTE e.g., pulmonary embolism and deep vein thrombosis • Awareness of what to do when an anticoagulant dose is missed • Understanding of which painkillers are the safest in combination with their anticoagulant • Drug-drug interactions and drug-food interactions with DOACS |
|--|

Throughout both patient and HCP resources, there is poor compliance with the EHRA criteria. [13] No counselling points are consistently mentioned throughout both patient and HCP resources. The EHRA has identified that the availability of multiple different DOAC resources often leads to uncertainty for physicians. [13] This uncertainty is amplified when these resources do not meet the EHRA criteria. The counselling aid we have developed is compliant with these guidelines and can overcome these uncertainties. The iPACT Guidelines’ criteria were found to be addressed in both HCP and patient resources to the same extent. However, similar to the EHRA guidelines, there was poor overall compliance with the iPACT criteria. [72]

5.5.3. Comparing Content of Patient and HCP Resources

The content of patient and HCP resources was compared based on the topics that they cover. Table 5-1 shows that patient resources have a greater focus on describing the medication and the condition being treated compared to HCP targeted resources. Patient resources are significantly more adherent to the EHRA criteria. This is likely due to the assumption that HCPs already have high knowledge levels and will be aware of points to raise during counselling, whereas patients require full counselling. As adherence to DOACs’ dosage regime is critical for their therapeutic effects, it would be expected that all resources refer to this; however, fewer than half of HCP resources detail what to do in the case of a missed dose. As seen in Table 5-2, side effects were covered in all but one patient resource, a much higher fraction than in HCP resources. This is concerning as pharmacists must counsel patients on possible side effects and what to do if they occur.

5.5.4. Readability

Overall, the readability statistics are similar across all patient resources researched. Simple, personal language was used in all patient resources, which is expected for this type of resource. The majority of resources lacked visual aids, which could compromise engagement with the material particularly for those with low literacy and health literacy levels. [220] The Flesch readability ease and Flesch-Kincaid grade level shows that the majority of patient resources would require a high school senior education level (17-18 years old or 6th year of secondary school education in Ireland) to understand the text. [209]

Furthermore, most Flesch-Kincaid grade levels are above the recommended grade of 8, with 62.5% having a grade between 9 and 11. However, it should be noted that there is potential for distortion of these scores by polysyllabic words such as 'anticoagulant' or 'anticoagulation' which are nonetheless potentially well understood by patients after an initial explanation; hence the importance of the additional readability parameters evaluated. There was no statistical difference in scores between patient resources from various sources, showing that all resources researched require a similar level of literacy to understand the information. Although many of these resources would be targeted at an older population due to the nature of drugs involved, low health literacy levels are associated with all ages and hence further simplification of patient leaflets and resources could be beneficial. While not determined here, a higher readability score is anticipated for HCP resources as HCPs are expected to have a higher degree of background knowledge and an understanding of medical jargon.

5.5.5. Comparing Content of Manufacturers and Non-Manufacturers Resources

Statistical analysis of manufacturer and non-manufacturer resources revealed that there was a statistically significant difference between the frequency at which “Missed dose/dosing errors”, “When to contact a HCP” and “Reasons why therapy may be suspended e.g., surgery” were identified. Eighteen of twenty-three manufacturer resources mention how to handle a missed dose, thus meeting EHRA guidelines, versus half of non- manufacturer resources. This may be due to the availability of clinical trial data to the former, which may have allowed them to identify a safe timeframe to take missed doses. It is important for patients to inform HCPs that they are taking a DOAC; this point is widely mentioned in manufacturer resources (16/23) versus non-manufacturer resources (20/43). Finally, less than half of non-manufacturer resources mention reasons why therapy may be stopped, thus failing to meet iPACT recommendations. Eighteen of twenty-three manufacturer resources meet this criterion. It appears that manufacturers’ resources

may be superior at providing certain information that is valuable to patients and as such should be preferentially signposted.

5.5.6. Policy, Practice, Research Implications

The counselling aid was developed from assessing the quality of counselling resources for DOACs and allows for improved patient counselling. Pharmacists can refer to this aid to recall the important points prior to counselling a patient on their DOAC. Patients with poor knowledge of their medication often have poor adherence. [215]

Salmasi *et al.*'s investigation of AF patients' knowledge gaps found that patients lack understanding of their condition and how to recognise symptoms of AF, which is a considerable worry for them. [215] In relation to anticoagulant medications, it was found that patients often struggle to understand bleeding risk and how to comprehend this risk versus the benefits of treatment. As already mentioned, patient resources and manufacturer resources are more likely to discuss these points and should be signposted to patients seeking more information about their condition and medication. The latter should be referred to by HCPs providing education/counselling to patients.

5.5.7. Strengths and Limitations

To our knowledge, a review of this kind has not previously been conducted for DOAC patient counselling resources. Key strengths of the study were the combination of a content audit with evaluation of readability, and the evaluation of readability across multiple dimensions rather than solely relying on readability scores which, while widely used, only represent one aspect of readability. However, the findings of this study must be seen considering some limitations. The first is that resources used were limited to those in English, and those freely available online. We cannot assume that the results are representative of all DOAC counselling materials. No validated audit tool for counselling on DOACs exists. However, the EHRA and iPACT recommendations against which the resources were audited were both developed and refined by international expert groups and are widely recognized. [13, 72] Nonetheless, local variation in DOAC guidelines, particularly in non-English speaking countries, is to be expected. It should also be noted that some of the resources may have been published before the EHRA and iPACT guidelines were issued, and therefore their publishers would not have had the benefit of this guidance.

5.5.8. Recommendations for Future Work

It is important to recognise that the usefulness of patient resources does not depend solely on their quality but is also influenced by individual patients' literacy and health literacy. Future work should

trial such resources in patients drawn from the target population to determine understanding, acceptability, and impact. The development and evaluation of visually rich aids targeted at patients with the most common indications for DOACs (atrial fibrillation and venous thromboembolism), formatted as single page infographics and detailing the main counselling points clearly whilst adhering to good health literacy principles, are likely to be of particular benefit to vulnerable patient groups. There is the potential for increased reliance on patient counselling resources such as those studied here during the COVID-19 pandemic due to decreased contact time for counselling and a suboptimal counselling environment. It would be beneficial to explore further the specific factors, such as socioeconomic background, which may help to predict increased counselling needs and the information that presents the greatest challenge to these patients, so that pharmacists can focus particular attention on counselling for these cohorts.

Similarly, provision of comprehensive guidance to pharmacists on the counselling points to be covered is not a guarantee of their successful communication and future work is needed to explore the optimal way in which provision of such information, tailored to individual patients' needs, can be integrated into the workflow of busy practitioners.

5.6. CONCLUSIONS

The content quality of the resources was determined based on their compliance with the recommendations in EHRA and iPACT guidelines. [13, 72] Patient resources were more likely to comply with the EHRA recommendations compared to HCP resources. Resources aimed at HCPs showed less uniformity; individual resources may be aimed at distinct stages of patient care thus leading to less homogeneity. Patient resources generally focus on describing the medication, the medical condition, and the medication's benefits and side effects. Several studies show that such information is essential for patients. [5] Manufacturer resources are more comprehensive for both HCPs and patients, with greater inclusion of information outlined in the EHRA and iPACT guidelines compared to non-manufacturer resources. Clear differences were found between patient and HCP resources in terms of the frequency at which certain counselling points are discussed. Patient resources exclusively used personal language however most resources had readability grade levels above the recommended grade 8.

In conclusion, it was found that although patient resources are generally compliant with the EHRA and iPACT guidelines, HCP resources are not. [13, 72] This, along with the vast number of resources available to HCPs and the limited time available, can lead to uncertainty during counselling. The counselling aid that we have developed (Counselling Aid for Pharmacists) is compliant with the

5. Quality of Counselling Resources for DOACs

EHRA and iPACT guidelines and thus provides pharmacists with a useful prompt of both the topic areas to address and the relevant information for each drug, which it is hoped will ultimately enhance patient education leading to improved patient outcomes.

6. Development of a Personalisable, Electronic Counselling Aid

6.1. INTRODUCTION

The number of monthly active smartphone users in Ireland is expected to reach 3.8 million by 2024 (74.85% of the total anticipated population), which would be an increase of approximately 400,000 users since 2018. The majority of internet users in Ireland use their smartphone for search engines, emails and to use social media sites at least weekly. Among adults aged 55 years and older smartphone penetration has increased by 34% from 2012 to 2019. [221] Recent reports predict a tremendous increase of smartphone usage across the world during the COVID-19 pandemic. [222]

The WHO acknowledged the potential in mHealth in a mobile health summit in 2011. The presentation noted that a more strategic approach to the planning, development and evaluation was required to further increase the impact of mHealth. [161] The WHO then went on to develop a National eHealth Strategy Toolkit to reflect the growing impact that eHealth brings to the delivery of healthcare around the world, increasing the efficiency of health systems and being more responsive to people's needs and expectations. The WHO defines eHealth as the use of information and communication technologies (ICT) for health. [223]

eHealth Ireland is an organisation within the HSE founded in 2015. [224] In the eHealth Strategy for Ireland document published, eHealth Ireland acknowledge the strain that healthcare systems are under to meet current demand, and anticipate this struggle will continue, with the population and chronic disease forecast to increase future service demands, unless eHealth innovation is introduced. [225]

Attitudes amongst health and social care professionals in Ireland towards telehealth were gathered in a national survey conducted in October 2020 by the HSE National Telehealth Steering Group. Over eight out of ten respondents indicated that online supports and therapy can enable a greater reach into the population. Some concerns included the need for updated IT systems, and increased administration support for clinical staff. [226]

As demonstrated in Chapter 4 – a review of RCTs using electronic education for patients on OACs produced promising results. [7-11] However, there is a need for future research of better quality, with larger sample sizes to thoroughly evaluate the impact of such interventions.

6.2. AIM AND OBJECTIVES

6.2.1. Aim

To create a novel, electronic counselling aid for DOAC patients, ready for piloting and subsequent use in a RCT.

6.2.2. Objectives

- To design a novel DOAC educational tool using technology that enables personalised patient education; and
- To identify the primary counselling points for patients using DOACs

6.3. METHODS

6.3.1. Content Design: Establishing the Primary Counselling Points

Educational video content was developed based on best practice as articulated in EHRA guidance and clinical experience. In order to develop a well-rounded and effective educational tool, the team first had to establish the primary counselling points that would be included in the video. This began with a review of the appropriate literature. As seen in Chapter 5, it was important to assess the quality of counselling resources published previously. Without a single, definitive audit standard for this topic, recommendations of two leading international bodies were utilised: the EHRA and the iPACT. [13, 72] The counselling points initially considered were:

- An introduction to the bleeding/clotting process
- What AF/VTE is
- How patients could potentially detect AF
- Consequences of AF/VTE
- Medication's purpose in AF/VTE
- Risk factors for AF/VTE
- Why anticoagulants are prescribed in AF/VTE
- DOAC specific information
 - Apixaban
 - Dabigatran
 - Rivaroxaban
 - Edoxaban

6. Development of a DOAC Educational Video Tool

- Importance of taking DOACs at the same time every day, and what to do if you forget a dose/take too much DOAC
- Side effects of DOACs – minor and major bleeding
- Drug interactions with DOACs
- Women of childbearing potential – specific advice
- What to do if you need an operation/procedure while taking DOACs
- Any monitoring required
- PILs/Patient alert cards
- Any questions/follow up

These counselling points were developed into a conversational-style script, and rough visuals were developed for each scene using simple drawings.

The research team who have experience and expertise in counselling patients taking DOACs in the AF clinic and in AMU in TUH went through the individual counselling points, ensuring plain English was used throughout, and that any similes used in their practice that patients previously found helpful were incorporated into the educational video. After a total of four counselling drafts, the final version was produced. The script was assessed for its readability using the Flesch Reading Ease score and Flesch-Kincaid grade level. [209]

The final main points covered within the educational video are as follows:

- What is AF/DVT/PE
- Risk factors
- The role of anticoagulants in AF/DVT/PE
- Information if patient is switching from warfarin to a DOAC
- Information if patients is currently taking antiplatelets such as aspirin or clopidogrel
- Counselling for each individual DOAC (apixaban, dabigatran, rivaroxaban, edoxaban)
 - How to pronounce the medicine's name
 - How to take it
 - Taking it every day
- Side effects of DOACs – minor and major bleeds
- How to reduce the risk of bleeds
- Missing a dose of DOAC
- Taking too much DOAC

- Informing a HCP before a procedure/surgery/dentist
- Drug interactions
- Food/drink interactions
- Monitoring whilst taking a DOAC
- PIL/Patient alert card
- Signs of stroke
- Informing friends and family
- Women of childbearing potential – specific advice

Table 6-1: EHRA and iPACT guidelines compared to video script [13, 72]

Essential Counselling Points from EHRA and iPACT Guidelines	Counselling Points Covered in Our Script
Indication or Reason for Taking DOAC	✓
Mechanism of Action	✓
Missed Doses/Dosing Errors	✓
Drug Interactions	✓
Bleeding/Trauma or Side Effects	✓
Informing a HCP Before Procedures or Reasons Therapy May be Suspended	✓
When to Contact a HCP or What to do in an Emergency/Patient Alert Card	✓
Monitoring	✓
Risks of Treatment	✓
Benefits of Treatment	✓
Preventing Complications	✓
Duration of Treatment	✓
Food Intake	✓

6.3.2. Graphic Design: Creation of the Electronic Counselling Aid

The electronic educational tool was developed using Cartoon Animator 4 (version 4.4.2408.1, Reallusion, New York, USA), and collated within a framework developed using Articulate 360 (version 3.49.24347.0, New York, USA). Each scene was animated through Cartoon Animator 4, using the inbuilt characters. The conversation between the pharmacist and the patient was recorded by the researcher and volunteers.

6.3.3. Presentation of the Counselling Aid

Different building blocks of scenes were prepared to accommodate variations in the DOAC prescribed (drug and regimen), indication (AF, PE or DVT) and patient demographics (gender).

6. Development of a DOAC Educational Video Tool

These building blocks are then collated as appropriate for individual patients when relevant menu selections are made by the healthcare professional providing counselling. Additional components were drawn using Photopea Image Editor, which links to Cartoon Animator 4 for importing. Each individual scene was then rendered and uploaded to Articulate 360.

It was decided that the selection of the patient variables would be completed at the beginning of the educational video by the healthcare professional. This would avoid any errors being made by the patient choosing options not related to them, and viewing educational content that didn't correlate with their condition. HCPs would choose the patient's condition (AF, DVT, or PE), their gender (male or female), whether they have taken warfarin previously or not, whether they have taken aspirin previously or not, and finally, which DOAC they have been prescribed. This gathers the sequence of educational content as a singular video for each patient, depending on the options selected.

6.4. RESULTS

Access to finalised version of the DOAC educational video may be granted on request.

6.4.1. Key Elements

The screen shown in Figure 6.1 allows the HCP to select the patient variables that apply. Such as, whether the patient is male or female, which will decide whether the video contains a male or female patient. The condition (AF, DVT, or PE), decides what counselling the patient will receive. If the option for warfarin is selected, patients will hear a brief explanation regarding the difference between warfarin and DOACs, and why their prescriber may have switched their treatment.

The screenshot shows a mobile application interface titled 'Trial' with a 'RESOURCES' link in the top right. The main content area is titled 'Please Select the Patient Options (One Option Per Line):'. Below this title, there are several blue buttons arranged in a grid. The first row contains 'Male' and 'Female'. The second row contains 'Atrial Fibrillation', 'Deep Vein Thrombosis', and 'Pulmonary Embolism'. The third row contains 'Warfarin' and 'No Warfarin'. The fourth row contains 'Aspirin' and 'No Aspirin'. The fifth row contains 'Apixaban', 'Dabigatran', 'Rivaroxaban', and 'Edoxaban'. At the bottom left is a gear icon, and at the bottom right are left and right arrow icons.

Figure 6.1: Screen for HCP to Select Patient Variables

6. Development of a DOAC Educational Video Tool

To facilitate comprehension, the CC button can be selected which includes closed captions throughout the video. Moving through the video can be done using the “previous” and “next” arrows to the left and the right of the scene. These features can be seen in Figure 6.2.



Figure 6.2: Scene 1 Male Patient

The same features are shown in Figure 6.3, but with the female character as the patient. The scene design is simple, so that patients can focus on the information they are being given.

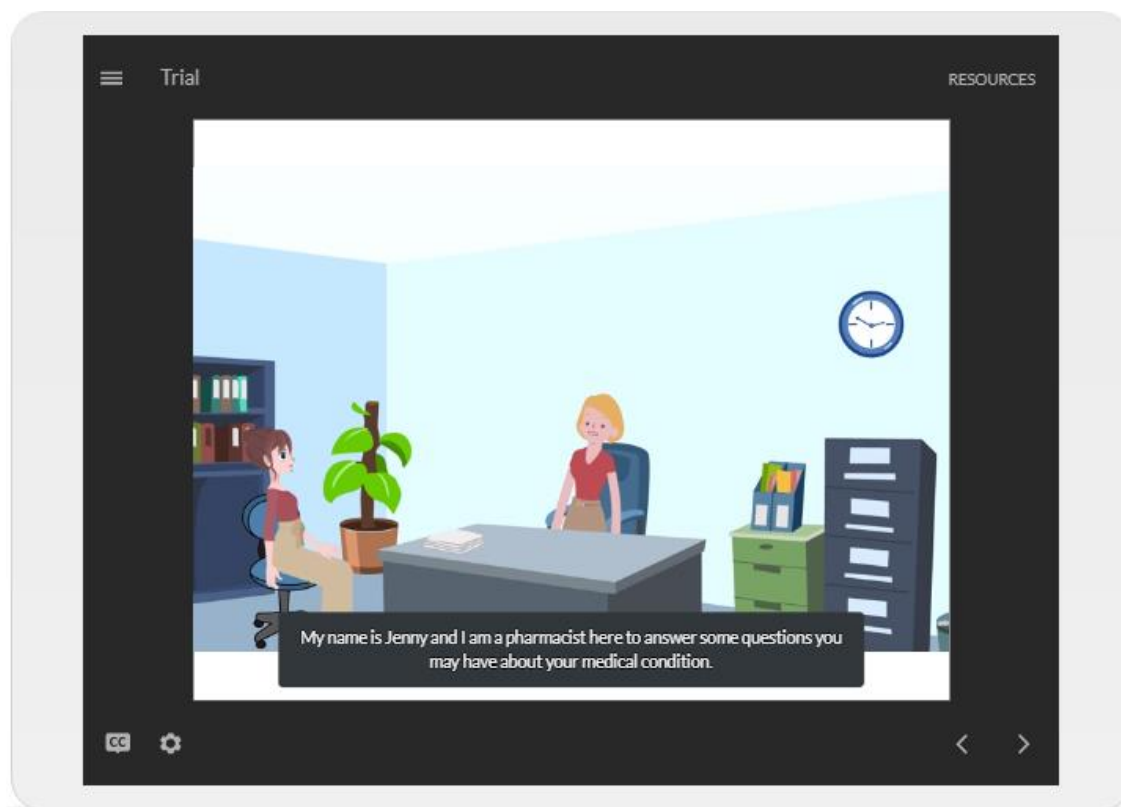


Figure 6.3: Scene 1 Female Patient

6.4.2. Duration of the Video

The videos shown can vary in duration, depending on the variables chosen. The longest duration of video for patients to watch is approximately 13 minutes. This features counselling points for females with AF, who have previously taken warfarin and aspirin, and have been prescribed the DOAC rivaroxaban. In contrast, the shortest duration of video is approximately 8 minutes 36 seconds. This video is personalised for males with DVT, having no previous history of warfarin or aspirin, and being prescribed apixaban.

6.4.3. Incorporation of Knowledge Test

The knowledge test developed in Chapter 3, once fully validated in the target population, will be incorporated into this educational aid. Patients will be able to complete the questionnaire on an iPad or tablet prior to viewing the educational video. This will provide a baseline knowledge level

for each patient. Following the educational video, the knowledge questionnaire will be inserted again for completion by the patient. Any knowledge gaps remaining can be addressed by the counselling HCP and the impact of the counselling aid can be evaluated.

6.4.4. Readability

The script produced for the educational video was assessed for its readability, using the Flesch reading ease score and the Flesch-Kincaid grade level. [209] The text for AF patients received a Flesch Reading Ease score of 71.2, indicating that the script is fairly easy to read. The Flesch-Kincaid grade level was 7th grade, which means that a 1st year student in secondary school in Ireland or a 12-13 year old should be able to understand the text. The script for DVT and PE patients was given a Flesch Reading Ease score of 68.8, meaning that it is standard/average. It has a Flesch-Kincaid grade level of 8th grade, or a 2nd year student in secondary school in Ireland or a 13-14 year old should comprehend the information.

6.5. DISCUSSION

6.5.1. Intended Use of the Counselling Aid

Prior to COVID-19, this video was to be used as an intervention in an RCT, conducted in TUH. This RCT aimed to compare counselling with the customisable electronic counselling aid versus usual care. Education for the intervention participants would be guided by knowledge gaps revealed by the knowledge test. Key educational points would always be reinforced by HCPs in TUH irrespective of the patient's questionnaire responses. The participants were to be patients over 18 years diagnosed with AF or DVT or PE taking DOACs. The primary outcome measure was to be the knowledge questionnaire scores pre and post counselling using the validated questionnaire described in Chapter 3. As regards secondary outcome measures, the time spent counselling by pharmacists, medication adherence at follow-up (using Morisky 8-item Medication Adherence Scale and DOAC prescription refill history at community pharmacy), and video access outside of the hospital (using personalised web access statistics). [227] Clinical outcomes would be measured through routine blood work and any adverse events such as hospitalisations would be recorded. It was also intended to gather qualitative data on patients' experience of counselling, determined by a brief exit interview, and staff members' experience of using the counselling aid in the RCT. An analysis of all the above parameters in light of patients' demographics would reveal the impact of the counselling aid.

6.5.2. Potential Advantages

6.5.2.1. Audio-visual Format and Readability

A potential advantage of this electronic counselling aid would be the use of audio-visual education techniques to enable education for patients with low literacy levels. [228] The Organisation for Economic Co-operation and Development (OECD) Adult Skills Survey shows that 17.9% or approximately 1 in 6 Irish adults are at or below level 1 on a 5 level literacy scale. At a level 1, adults may be unable to understand basic written information. This survey was conducted in 2012 and assessed 6,000 people between the ages of 16 to 65 in Ireland. Ireland is rate 15 out of 24 countries for literacy levels. Those aged 55 to 65 have the lowest average literacy score. [229]

Fleming *et al.*'s VARK theory of learning styles can be easily applied to patient education. The acronym VARK represents the Visual, Aural, Read or write, and Kinaesthetic modalities of learning. The majority of individuals may be multi-modal. [230] The electronic counselling aid would cater for both visual and aural learners. Standard interventions, such as leaflets would cater for patients that prefer to learn through written materials.

A study by Popoola *et al.* found that 43.6% of patients would like to learn about VTE through their doctor and supplemented by watching videos. [231]

Overall, the readability of the scripts for the educational video had positive scores. The script used simple, personal language throughout to enable understanding. It is worth noting that the Flesch Reading Ease score and Flesch grade level calculation could have been distorted due to the use of polysyllabic words such as "fibrillation", "embolism", "thrombosis", and "anticoagulant". These terms are described throughout the text to ensure comprehension. Education materials that are easier to read are more likely to be understood by patients. [232]

6.5.2.2. Availability of the Aid

Another advantage of the counselling aid is its availability of the content from home which allows for sharing of information with carers and family. This could be extremely valuable, particularly where multiple people share caring responsibilities. A study by Eames *et al.* found that some of the main barriers for patients and carers accessing information were not knowing what to ask, the information not being easy to understand and using medical jargon, healthcare professionals being too busy in hospitals, and limited communication among HCPs. Carers were found to have limited time to seek and access information. [233] By providing accessible, tailored information to both

patients and carers, our educational tool could enable the opportunity for both parties to participate in their healthcare.

The role of carers, particularly informal carers, is gaining increasing recognition. Building an effective partnership between carers and HCPs is essential to ensure carers are fully involved. A study by Knight *et al.* showed that carers generally assume significant responsibility for medicines administration. The majority of participants in the study (14/19) found that the information provided about medications by HCPs at discharge was not satisfactory, and that either no information was provided, or an assumption was made by the HCP that the patient or carer fully understood the medications received in the hospital. [234] Our educational aid has the potential to ensure effective transfer of information between HCP, patient and carers, especially upon discharge from the hospital.

6.5.2.3. Tailored Education

As seen in chapter 4, there is a need for further research using electronic counselling aids with adequate sample sizes, trialled in an RCT. Out of the five studies included in the electronic education for OAC patients review, only one of the interventions enabled the education to be tailored to the individual patient. [11] The electronic counselling aid developed in this chapter also allows for the education to be personalised to the patient.

The importance of providing patients with a tailored education is noted in the EHRA guidelines. [13] The 2020 ESC guidelines recommend the integrated management of AF patients. This requires patients' involvement and shared decision making among patients and their inter-disciplinary team. [171] To make informed and effective decisions, patients must be adequately educated. Patient knowledge is often limited, particularly when first diagnosed, when the majority of treatment decisions are made. [4, 5, 110, 153, 157] Desteghe *et al.* has shown that education focused on the knowledge gaps of the patient, significantly improved patient knowledge. [82, 85] The incorporation of our knowledge questionnaire with this counselling aid will allow HCPs to address the knowledge gaps revealed after the educational video, with the hopes of improving patient knowledge and other patient related outcomes.

When asked about what aspects of VTE patients would like to be educated on, most patients focused on VTE in the context of harm, such as prevention, risk factors, and consequences of VTE. [231] These areas are addressed in the counselling aid, but it is important for HCPs to ask their patients what their preferences are when providing patient-specific education.

6.5.2.4. Prompting Questions

The fact that patients will watch this educational video in the waiting room, prior to a consultation with a HCP, means they may be prompted to ask questions during the face-to-face consultation. Previous research has found prompt lists useful for patients and family members, which involves preparing a list of questions prior to meeting with a HCP. This can facilitate patient involvement and shared decision making during the consultation. [235] If patients realise that they have difficulties while answering questions in the knowledge questionnaire, they may ask their HCP about the topic during their discussion.

6.5.2.5. Gaining Insight into Common Knowledge Gaps

The use of this electronic counselling aid, which will incorporate the knowledge questionnaire, is expected provide HCPs with insight into aspects that patients commonly get wrong about their condition and DOAC treatment. For example, the JAKQ-VTE found that only 1 in 4 VKA patients, and 1 in 2 DOAC patients, knew what to do if they missed a dose of OAC. [5] Another study using the OAK test found that a knowledge deficit was obvious in the areas of vitamin K and drug interactions with warfarin, skipping dose management, and INR tests. [236] Gaining awareness of common knowledge gaps in DOAC patients could be valuable for HCPs frequently providing education.

6.6. CONCLUSION

The educational video developed throughout this chapter has the potential to aid the counselling of patients taking DOACs for AF, DVT, and PE. The timeline of this project was impacted by COVID-19, as increased restrictions throughout the country and particularly in hospitals, prevented the RCT from being conducted. Without trialling the tool in a highly powered randomised clinical trial of good quality, it is impossible to predict the impact of this novel intervention. Future work as described will be conducted using this tool and will be published in due course.

7. Summary, Overall Conclusions and Future Work

7.1. CHAPTER 1

This chapter provided a brief introduction to knowledge questionnaires and electronic counselling aids for patients taking DOACs, and the research already conducted on this. The basics of atrial fibrillation, deep vein thrombosis, and pulmonary embolism are outlined, including signs, symptoms, diagnosis and treatment. An overview and comparison of DOACs and warfarin was also provided in this section. Finally, the aims, objectives and importance of the research are described.

7.2. CHAPTER 2

A review of the literature regarding knowledge questionnaires for OAC patients was conducted in Chapter 2. Detailed electronic searches of the databases PubMed NLM, EMBASE, and the Cochrane Library were conducted to identify the relevant literature. Six papers were included that detailed the development and validation of knowledge questionnaires for patients taking OACs. [7-11] These tools were compared based on the anticoagulants assessed, intended use, format, content, validation methods and quality. More research is needed in this area to produce high quality validated knowledge questionnaires.

7.3. CHAPTER 3

The pilot study validation for of the knowledge questionnaire outlines the development and pilot validation of a knowledge questionnaire for DOAC patients. The processes involved included questionnaire development, content validation amongst an expert panel of healthcare professionals, and pilot validation in a patient cohort in TUH. The various versions of the questionnaire produced throughout this study are provided. This research was heavily impacted by COVID-19. Further research is required to conduct a full-scale validation of the knowledge questionnaire.

7.4. CHAPTER 4

A literature review of electronic education interventions for patients taking OACs is outlined in Chapter 4. Strategic searches of PubMed NLM, EMBASE and Google Scholar were completed to discover RCTs and quasi-RCTs that matched the inclusion criteria. Five studies were included in the review. [7-11] Risk of bias assessment was done for each study using Cochrane's risk of bias tool. [168] While the studies showed mostly positive outcomes for their electronic education

techniques, their small sample sizes mean that they are limited in their value. More adequately powered, good quality, RCTs are needed in this area of research.

7.5. CHAPTER 5

An overview of the quality of counselling resources for OAC patients is described in Chapter 5. Resources were assessed based on their content's compliance with the EHRA and iPACT guidelines, their readability based on Cosgrove's readability checklist and Flesch Reading Ease score, and their Flesch-Kincaid grade level. [13, 72, 208, 209]

Manufacturer and non-manufacturer resources, and patient and HCP resources, were compared based on their content. Based on this research, patient resources were more likely to comply with the EHRA guidelines than HCP resources. Manufacturer resources were more comprehensive for both patients and HCPs, and were more likely to comply with the EHRA and iPACT guidelines. Counselling resources should be assessed for their quality prior to their use to ensure effective patient education.

7.6. CHAPTER 6

Chapter 6 outlines the development of a novel, electronic, personalisable counselling aid for patients taking DOACs. The process involved content design to establish the main counselling points to be included, graphic design of the tool using Cartoon Animator 4, and the presentation concept of the aid using Articulate 360 software. Building blocks were created for each animated scene, and collated based on the selection of variables made by the HCP at the beginning of the tool. Further research is required to run an RCT using this counselling aid, incorporating the knowledge questionnaire, compared to usual care in the hospital setting to establish the intervention's impact. This research had been impacted by COVID-19 and unfortunately the planned RCT could not be conducted.

7.7. LIMITATIONS

A limitation of this research are the small patient numbers and the incomplete validation of the knowledge questionnaire, as outlined in chapter 3. The knowledge questionnaires should be put through a full-scale validation process, to properly evaluate and receive feedback on their effectiveness and reliability.

Additionally, the electronic counselling aid developed in chapter 6 should be assessed as an intervention in a RCT in the hospital setting. A RCT of good quality, with low risk of bias, and an adequate sample size would show the impact of this intervention.

7.8. FUTURE WORK

Future research should include a full-scale validation of the knowledge questionnaire in both AF and VTE patients, in different healthcare settings: community pharmacies and hospitals.

Also, a RCT conducted in the atrial fibrillation outpatient clinic and the AMU in TUH, Dublin. Patients' knowledge will be measured using the newly validated knowledge questionnaire for patients taking DOACs, before and after the electronic aid. This will provide a measure of baseline knowledge, and remaining knowledge gaps will be addressed by the counselling HCP. This intervention will be trialled against usual care. Outcomes measured will include knowledge levels, medication adherence, pharmacist counselling time, extent of video access by patients outside of the hospital, clinical outcomes via routine blood work, and adverse events such as hospitalisations. There is the potential to incorporate knowledge checks and recall practices such as quizzes during the counselling session to improve recall of essential material during the final knowledge assessment and in a patient's everyday life.

A focus group with HCPs who were involved in the RCT will provide valuable feedback on the intervention. This will reveal any indirect effects of the intervention such as providing HCPs with greater insights into the aspects of anticoagulation that patients find most challenging or which require most frequent reinforcement. HCPs who used the intervention could also provide suggestions for further refinement of the tool.

7.9. OVERALL CONCLUSIONS

The literature review in Chapter 4 revealed that previous work in this area consists of a small number of studies. The electronic educational interventions in the studies generally showed positive impacts for patients but the overall evidence is weak. The implication of this thesis is the successful development of a knowledge questionnaire tool for patients taking DOACs for AF or VTE. The team effectively ran a small-scale pilot study of the validation process of this tool, including content validation in an expert panel of healthcare professionals, and a pilot of the validation process in a small group of AF patients. Also, we developed a personalisable electronic educational tool for patients taking DOACs.

Overall, this thesis lays the foundation for conducting a full-scale validation study of the knowledge questionnaire, as well as a comprehensive randomised controlled trial to evaluate the impact of such tools on a range of clinical and non-clinical outcomes.

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Appendices

1. Summary Tables of Knowledge Questionnaires

Table 1-1: Summary Table of Knowledge Questionnaires

Questionnaires	AKA [1]	OAK [2]	AKT [3]	JAKQ [4]	JAKQ-VTE [5]	KODOA [6]	I-AKT [103]
Format	29-item, MCQ	23-item, MCQ	28-item, open-ended & MCQ	16-item, MCQ	16-item, MCQ	15-item, MCQ	28-item, open-ended & MCQ
Validation	60 patients	102 patients	49 patients	466 patients	273 patients	32 patients	113 patients
Setting	Outpatient secondary care	Mix of primary & outpatient secondary care	Primary care	Outpatient and inpatient secondary care	Inpatient secondary care	Primary care	Outpatient secondary care
Languages	English	English	English	Dutch	Polish	English	Italian
Year of Publication	2005	2006	2016	2016	2018	2018	2018
Self-administration or HCP	Self	Self	Self	Self	Self	Self	Self
Drug(s) assessed	Warfarin	Warfarin	DOACs & Warfarin	DOACs & Warfarin	DOACs & Warfarin	DOACs	DOACs & Warfarin

Table 1-2: Content Areas Recommended by the EHRA and iPACT Guidelines Covered in Validated Questionnaires [62, 63]

	AKA [1]	OAK [2]	AKT [3]	JAKQ [4]	JAKQ-VTE [5]	KODOA [6]
Indication or Reason for Taking DOAC	✓			✓	✓	✓
Mechanism of Action						✓
Missed Doses/Dosing Errors	✓		✓	✓	✓	✓
Drug Interactions	✓	✓	✓	✓	✓	✓
Informing a HCP Before Procedures	✓		✓	✓	✓	✓
When to Contact a HCP	✓		✓	✓	✓	✓
Monitoring	✓	✓	✓	✓	✓	✓
Benefits of Treatment	✓					
Risks of Treatment	✓	✓	✓	✓	✓	✓
How to Prevent Complications	✓		✓			
How to Act in an Emergency/Patient Alert Card	✓		✓	✓	✓	✓
Duration of Therapy			✓			✓
Food Intake	✓	✓				
Side Effects or Bleeding/Trauma	✓	✓	✓	✓	✓	✓
Reasons Why Therapy May Be Suspended e.g., Surgery	✓		✓	✓	✓	✓

Table 1-3: Validation Methods Used for Knowledge Questionnaires

	AKA [1]	OAK [2]	AKT [3]	JAKQ [4]	JAKQ-VTE [5]	KODOA [6]
Content Validation	✓	✓	✓	✓	✓*	✓
Face Validation				✓		✓
Response Process				✓		
Construct Validity	✓	✓	✓	✓		✓
Reliability	✓	✓	✓	✓		✓
Sensitivity Testing				✓	✓	✓
Discriminatory Potential		✓	✓	✓		✓**

*The choice of questions was discussed by investigators to reach consensus.

** Item discrimination was calculated using the difference for each item answered correctly in the lowest vs. the highest quartile.

2. Questionnaires

Table 2-1: The Original Jessa Atrial Fibrillation Knowledge Questionnaire (JAKQ)[4]

The Jessa Atrial fibrillation Knowledge Questionnaire

1. Questions about atrial fibrillation in general

- 1.1 What is meant by atrial fibrillation?
- ☒ A condition where the heart beats irregularly and often faster than normal
 - ☐ A heart muscle disease through which the heart is unable to pump enough blood through the body
 - ☐ A blood disorder causing the development of clots in the heart
 - ☐ I do not know
- 1.2 Is atrial fibrillation always accompanied by symptoms?
- ☐ Yes
 - ☐ Yes, but only in patients with a certain degree of heart failure
 - ☒ No
 - ☐ I do not know
- 1.3 What can you do to detect atrial fibrillation?
- ☐ Nothing, atrial fibrillation is very difficult to detect and only a doctor can recognise the condition
 - ☒ I can detect atrial fibrillation by taking my pulse regularly
 - ☐ By doing an atrial fibrillation urine test. I can get one at the chemist's
 - ☐ I do not know
- 1.4 What are the consequences of atrial fibrillation?
- ☐ It has no harmful effects
 - ☒ It can cause blood clots which can lead to stroke (cerebral infarction)
 - ☐ It can lead to increased blood pressure, causing the body to retain fluid
 - ☐ I do not know
- 1.5 Medication can:
- ☐ Permanently prevent atrial fibrillation, so that the arrhythmia will never come back
 - ☐ Largely prevent atrial fibrillation: the arrhythmia will only occur sporadically
 - ☒ Not prevent atrial fibrillation permanently, as the arrhythmia will increasingly occur with ageing, even when taking medication
 - ☐ I do not know
- 1.6 Should I go to the general practitioner or emergency room each time I feel atrial fibrillation?
- ☐ Yes
 - ☒ No
 - ☐ Only at night or on the weekend
 - ☐ I do not know
- 1.7 Being overweight:
- ☒ Exacerbates atrial fibrillation
 - ☐ Has no effect on atrial fibrillation
 - ☐ Protects against atrial fibrillation
 - ☐ I do not know
- 1.8 Why are blood thinners often prescribed for patients with atrial fibrillation?
- ☐ In order to prevent the body from retaining fluid
 - ☒ In order to prevent the development of blood clots in the heart, which can lead to stroke
 - ☐ In order to allow blood to flow more easily throughout the body and hence lower blood pressure
 - ☐ I do not know

2. Questions about blood thinners (oral anticoagulants)

- 2.1 When should I take my blood thinners?
- ☐ I should only take blood thinners if I have had a stroke
 - ☐ Only when I feel atrial fibrillation, for one week
 - ☒ I should always take my blood thinners, even if I do not feel atrial fibrillation
 - ☐ I do not know
- 2.2 Possible side effects of blood thinners are:
- ☐ Headaches and dizziness
 - ☐ A too low or too high blood pressure
 - ☒ The occurrence of bleedings and longer bleeding times in case of injuries
 - ☐ I do not know
- 2.3 Which painkillers may I take?
- ☐ Any painkiller
 - ☒ Medication based on paracetamol: e.g. Panadol (*examples of common brand names can be inserted*)
 - ☐ One of the following anti-inflammatory agents: e.g. Aspirin, Ibuprofen (*examples of common drugs can be inserted*)
 - ☐ I do not know
- 2.4 What should I do if I regularly have minor nose bleeds (that spontaneously cease)?
- ☐ I should stop taking my blood thinner
 - ☒ I should contact the general practitioner or specialist, while continuing to take my blood thinners
 - ☐ I should go to the emergency service
 - ☐ I do not know
- 2.5 What if I need an operation?
- ☐ I can go on taking my blood thinners
 - ☒ I should discuss my options with the doctor
 - ☐ I should stop taking my blood thinners one week in advance
 - ☐ I do not know

3. Questions about vitamin K antagonists (VKA)

- 3.1 How often should I have my blood thinning checked?
- ☒ At least once a month
 - ☐ twice a year
 - ☐ once a year
 - ☐ I do not know
- 3.2 What if I have forgotten to take my blood thinner?
- ☒ I should still take my forgotten pill (immediately or at the next dose)
 - ☐ I should skip that dose and wait until the next dose
 - ☐ I should take a regular aspirin instead
 - ☐ I do not know
- 3.3 What does INR (international normalized ratio) mean?
- ☐ It is a measure to check how well my kidneys work
 - ☐ It is a measure to check whether I have anemia
 - ☒ It is a measure to check how thick or how thin my blood is
 - ☐ I do not know

3. Questions about new blood thinners (non-vitamin K antagonist oral anticoagulants: NOACs)

- 3.1 It is important that I take my blood thinner at the same time every day.
- ☒ Yes
 - ☐ No
 - ☐ No, as long as it is between meals
 - ☐ I do not know
- 3.2 What if I have forgotten to take my blood thinner?
- ☒ I should still take that dose, unless the time till my next dose is less than the time after my missed dose
 - ☐ I should skip a dose and wait until the next dose
 - ☐ I should take two pills at the next dose
 - ☐ I do not know
- 3.3 My blood thinner comes with a card:
- ☐ On which I indicate when I take the blood thinner
 - ☒ Which I have to show to my general practitioner and specialist
 - ☐ Which I have to give to the pharmacist so that she/he can give me the right medication
 - ☐ I do not know

Table 2-2: Version 1.0 of the Questionnaire for AF patients

1. Questions about AF in general
1.1. What is meant by atrial fibrillation? ☐ A condition where the heart beats irregularly and often faster than normal ☐ A heart muscle disease through which the heart is unable to pump enough blood through the body ☐ A blood disorder causing the development of clots in the heart ☐ I do not know
1.2. Is atrial fibrillation always accompanied by symptoms? ☐ Yes ☐ Yes, but only in patients with a certain degree of heart failure ☐ No ☐ I do not know
1.3. What can you do to detect atrial fibrillation? ☐ Nothing, atrial fibrillation is very difficult to detect and only a doctor can recognise the condition ☐ I can detect atrial fibrillation by taking my pulse regularly ☐ By doing atrial fibrillation urine test. I can get one at the chemist's ☐ I do not know
1.4. What are the consequences of atrial fibrillation? ☐ It has no harmful effects ☐ It can cause blood clots which can lead to stroke (cerebral infarction) ☐ It can lead to increased blood pressure, causing the body to retain fluid ☐ I do not know

1.5. Should I go to the general practitioner or emergency room each time I feel atrial fibrillation

- ☐ Yes
- ☐ **No**
- ☐ Only at night or on the weekend
- ☐ I do not know

1.6. Being overweight:

- ☐ **Exacerbates atrial fibrillation**
- ☐ Has no effect on atrial fibrillation
- ☐ Protects against atrial fibrillation
- ☐ I do not know

1.7. Why are blood thinners often prescribed for patients with atrial fibrillation?

- ☐ In order to prevent the body from retaining fluid
- ☐ **In order to prevent the development of blood clots in the heart, which can lead to stroke**
- ☐ In order to allow blood to flow more easily throughout the body and hence lower blood pressure
- ☐ I do not know

2. Questions about blood thinners (oral anticoagulants)

2.1. When should I take my blood thinner?

- ☐ I should only take blood thinner if I had a stroke
- ☐ Only when I feel atrial fibrillation, for one week
- ☐ **I should always take my blood thinner, even if I do not feel atrial fibrillation**
- ☐ I do not know

2.2. Possible side effects of blood thinners are:

- ☐ Headaches and dizziness
- ☐ A too low or too high blood pressure
- ☐ **The occurrence of bleedings and longer bleeding times in case of injuries**
- ☐ I do not know

2.3. Which painkillers may I take? ☐ Any painkiller ☐ Medication based on paracetamol: e.g. Panadol ☐ One of the following anti-inflammatory agents: Aspirin (Disprin), Ibuprofen (Nurofen), Diclofenac (Difene) ☐ I do not know
2.4. What should I do if I regularly have minor nose bleeds (that spontaneously cease)? ☐ I should stop taking my blood thinner ☐ I should contact the general practitioner or specialist while continuing to take my blood thinner ☐ I should go to the emergency services ☐ I do not know
2.5. What if I need an operation? ☐ I can go on taking my blood thinner ☐ I should discuss my options with the doctor ☐ I should stop taking my blood thinner one week in advance ☐ I do not know
3. Questions about new blood thinners (DOACs)
3.1. Is it important that I take my blood thinner at the same time every day? ☐ Yes ☐ No ☐ No, as long as it is in between meals ☐ I do not know
3.2. What if I have forgotten to take my blood thinner? ☐ I should still take that dose, unless the time till my next dose is less than the time after my missed dose ☐ I should skip a dose and wait until the next dose ☐ I should take two pills at the next dose ☐ I do not know

3.3. My blood thinner comes with a card:

- ☐ On which I indicate when I take the blood thinner
- ☐ **Which I have to show to my general practitioner and specialist**
- ☐ Which I have to give to the pharmacist so that she/he can give me the right medication
- ☐ I do not know

Table 2-3: Version 1.0 of the Questionnaire for DVT and PE patients

1. Questions about DVT
1.1. What is meant by DVT? ☐ A condition that makes the blood less able to clot, causing the sufferer to bleed severely from even a slight injury ☐ A blood clot that has formed in one of the blood vessels that lie far inside the muscles, usually of the leg ☐ A condition in which there is not enough red cells in the blood, causing tiredness and weakness ☐ I do not know
1.2. Is DVT always accompanied by pain or swelling of the arms or legs? ☐ Yes ☐ Yes, but only in patients with severe DVT ☐ No ☐ I do not know
1.3. What are the consequences of DVT? ☐ DVT has no harmful effects ☐ DVT can lead to a clot in the lungs (PE) or brain (stroke) ☐ DVT can lead to increased blood pressure ☐ I do not know

1. Questions about PE

1.1. What is meant by PE?

- ☐ **PE occurs when blood vessels in the lungs are partially blocked, most often by clots**
- ☐ PE happens when the inside walls of the lungs become inflamed and swollen, causing difficulty breathing
- ☐ PE occurs when your heart muscle does not get enough oxygen-rich blood, due to decreased blood flow to the heart
- ☐ I do not know

1.2. Is PE always accompanied by pain or shortness of breath?

- ☐ Yes
- ☐ Yes, but only in patients with severe PE
- ☐ **No**
- ☐ I do not know

1.3. What are the consequences of PE?

- ☐ PE has no harmful effects
- ☐ **PE can lead to a clot in the brain (stroke)**
- ☐ PE can lead to increased blood pressure
- ☐ I do not know

2. Questions about VTE in general (given to both DVT and PE)
2.1. Medication called DOACs can: ☐ Ensure you will never experience a blood clot again ☒ Treat a DVT/PE whilst you take the medicine ☐ Lower your blood pressure ☐ I do not know
2.2. One factor that can increase the risk of DVT/PE is: ☐ Increased physical activity ☒ Travel by air or car for more than 6-8 hours ☐ Reduced caffeine intake ☐ I do not know
2.3. Being overweight: ☐ Has no effect on DVT/PE ☒ Increases the risk of DVT/PE ☐ Protects against DVT/PE ☐ I do not know
2.4. How long should DOACs be taken for? ☐ Until I am released from hospital ☒ DOACs should be used always, for at least 3 months after diagnosis ☐ Only for one week after diagnosis of DVT/PE ☐ I do not know
3. Questions about blood thinners (oral anticoagulants) for DVT and PE patients
3.1. When should I take my blood thinner? ☐ I should only take my blood thinner if I have a stroke ☐ Only when I feel the symptoms of DVT/PE ☒ I should always take my blood thinner, even if I do not feel any symptoms ☐ I do not know

3.2. Possible side effects of blood thinners are: ☐ Headaches and dizziness ☐ A too low or too high blood pressure ☐ The occurrence of bleedings and longer bleeding times in case of injuries ☐ I do not know
3.1. Which painkillers may I take? ☐ Any painkiller ☐ Medication based on paracetamol: e.g. Panadol ☐ One of the following anti-inflammatory agents: Aspirin (Disprin), Ibuprofen (Nurofen), Diclofenac (Difene) ☐ I do not know
3.2. What should I do if I regularly have minor nose bleeds (that spontaneously cease)? ☐ I should stop taking my blood thinner ☐ I should contact the general practitioner or specialist while continuing to take my blood thinner ☐ I should go to the emergency services ☐ I do not know
3.3. What if I need an operation? ☐ I can go on taking my blood thinner ☐ I should discuss my options with the doctor ☐ I should stop taking my blood thinner one week in advance ☐ I do not know
4. Questions about new blood thinners (DOACs)
4.1. Is it important that I take my blood thinner at the same time every day? ☐ Yes ☐ No ☐ No, as long as it is in between meals ☐ I do not know

4.2. What if I have forgotten to take my blood thinner?

- ☐ **I should ask my doctor, nurse, or pharmacist, or read the leaflet that comes with my blood thinner**
- ☐ I should skip a dose and wait until the next dose
- ☐ I should take two pills at the next dose
- ☐ I do not know

4.3. My blood thinner comes with a card:

- ☐ On which I indicate when I take the blood thinner
- ☐ **Which I have to show to my general practitioner and specialist**
- ☐ Which I have to give to the pharmacist so that she/he can give me the right medication
- ☐ I do not know

Table 2-4: Version 2.0 of the Questionnaire for AF patients

Questionnaire

Please choose **ONE** correct answer per question by circling the option (A, B, C, or D).

If you do not know the correct answer, please choose "I do not know".

Questions about Atrial Fibrillation (AFib) in general

1. What is meant by AFib?
 - A. A condition where the heart beats irregularly and often faster than normal
 - B. A heart muscle disease where the heart is too weak to pump enough blood around the body
 - C. A disease of the blood causing blood clots in the heart**
 - D. I do not know
2. Will I always feel symptoms with AFib?
 - A. Yes
 - B. No**
 - C. I do not know
3. What can I do to detect AFib?
 - A. Nothing, AFib is very hard to detect and only a doctor can recognise it
 - B. I could possibly detect AFib by taking my pulse twice a day for two weeks and noting the result**
 - C. By doing an AFib urine test which I can get at the pharmacy
 - D. I do not know
4. What are the possible effects of AFib?
 - A. It has no harmful effects
 - B. It can cause blood clots which can then cause a stroke**
 - C. It can cause high blood pressure, and the body will retain fluid
 - D. I do not know
5. DOACs can:
 - A. Stop AFib, so that it will never come back
 - B. Mostly stop AFib: It will only occur sometimes
 - C. Reduce the risk of serious stroke in AFib**
 - D. I do not know
6. Should I go to the doctor each time I feel AFib?
 - A. Yes
 - B. No**
 - C. I do not know

7. Being overweight:
- A. **Can increase the risk of AFib**
 - B. Has no effect on AFib
 - C. Protects against AFib
 - D. I do not know
8. What factors can increase the risk of AFib?
- A. Eating a Mediterranean diet of oily fish, vegetables, fruit etc.
 - B. **Smoking, too much alcohol intake, and having high blood pressure**
 - C. Moderate exercise or physical activity
 - D. I do not know
9. Why are anticoagulants (blood thinners) often prescribed for patients with AFib?
- A. To prevent fluid retention
 - B. **To reduce the risk of stroke**
 - C. To lower blood pressure
 - D. I do not know

Questions about Direct Oral Anticoagulants (DOACs)

10. When should I take my DOAC?
- A. I should only take my DOAC if I have a stroke
 - B. I should only take my DOAC when I feel signs of AFib
 - C. **I should always take my DOAC as prescribed, even if I do not feel symptoms of AFib**
 - D. I do not know
11. Possible side effects of DOACs are:
- A. Headaches and dizziness
 - B. Low blood pressure
 - C. **Easy bruising or bleeding**
 - D. I do not know
12. Which painkillers are safe to take with DOACs?
- A. Any painkiller
 - B. **Painkillers containing paracetamol**
 - C. One of the following anti-inflammatory painkillers: Aspirin or ibuprofen
 - D. I do not know
13. What should I do if I often have minor nose bleeds (that stop on their own)?
- A. I should stop taking my DOAC
 - B. **I should contact my doctor while I keep taking my DOAC**
 - C. I should go to the hospital
 - D. I do not know

14. What should I do if I experience a major bleed, e.g. coughing up blood?
 - A. I should stop taking my DOAC
 - B. I should wait for a day to see if it stops
 - C. I should call my doctor straight away**
 - D. I do not know
15. What if I need an operation?
 - A. I should keep taking my DOAC
 - B. I should discuss my DOAC with the doctor**
 - C. I should stop taking my DOAC one week before the operation
 - D. I do not know
16. Is it important to take my DOAC at the same time every day?
 - A. Yes**
 - B. No
 - C. I do not know
17. What should I do if I forget to take my DOAC?
 - A. I should ask my doctor, nurse or pharmacist, or read the leaflet that comes with my DOAC**
 - B. I should always skip that dose and wait until the next dose
 - C. I should always take a double dose at the next dose time
 - D. I do not know

About you

18. My age is: _____ years
19. My gender is:
 - A. Male
 - B. Female
 - C. Other: _____
20. The highest level of education I have reached is:
 - A. Primary school
 - B. Secondary school
 - C. Third level (undergraduate qualification)
 - D. Third level (postgraduate qualification)
21. Besides my DOAC, I take the following other prescribed medicine(s):
 (Please list, if any, or otherwise state 'None'.)

Table 2-5: Version 2.0 of the Questionnaire for DVT patients

Questionnaire

Please choose **ONE** correct answer per question by circling the option (A, B, C, or D).

If you do not know the correct answer, please choose "I do not know".

Questions about Deep Vein Thrombosis (DVT) in general

1. **What is meant by DVT?**
 - A. A condition that makes the blood less able to clot, causing easy bleeding
 - B. A blood clot in a blood vessel, most commonly in the leg muscle**
 - C. A condition where there is not enough iron in the blood, causing tiredness
 - D. I do not know
2. **Will I always feel symptoms with DVT?**
 - A. Yes
 - B. No**
 - C. I do not know
3. **DOACs can:**
 - A. Ensure you will never have a blood clot again
 - B. Make a blood clot much less likely to happen
 - C. Lower your blood pressure
 - D. I do not know
4. **Being overweight:**
 - A. Can increase the risk of DVT**
 - B. Has no effect on DVT
 - C. Protects against DVT
 - D. I do not know
5. **What factors can increase the risk of DVT?**
 - A. Eating a Mediterranean diet of oily fish, vegetables, fruit etc.
 - B. Smoking, immobility, and taking combined oral contraceptive pills**
 - C. Moderate exercise or physical activity
 - D. I do not know

Questions about Direct Oral Anticoagulants (DOACs)

6. **When should I take my DOAC?**
 - A. I should only take my DOAC if I have a stroke
 - B. I should only take my DOAC when I feel signs of DVT
 - C. I should always take my DOAC as prescribed, even if I do not feel symptoms of DVT**
 - D. I do not know
7. **Possible side effects of DOACs are:**
 - A. Headaches and dizziness
 - B. Low blood pressure
 - C. Easy bruising or bleeding**
 - D. I do not know
8. **Which painkillers are safe to take with DOACs?**
 - A. Any painkiller
 - B. Painkillers containing paracetamol**
 - C. One of the following anti-inflammatory painkillers: Aspirin or ibuprofen
 - D. I do not know
9. **What should I do if I often have minor nose bleeds (that stop on their own)?**
 - A. I should stop taking my DOAC
 - B. I should contact my doctor while I keep taking my DOAC**
 - C. I should go to the hospital
 - D. I do not know
10. **What should I do if I experience a major bleed e.g. coughing up blood?**
 - A. I should stop taking my DOAC
 - B. I should wait for a day to see if it stops
 - C. I should call my doctor straight away**
 - D. I do not know
11. **What if I need an operation?**
 - A. I should keep taking my DOAC
 - B. I should discuss my DOAC with the doctor**
 - C. I should stop taking my DOAC one week before the operation
 - D. I do not know

12. Is it important to take my DOAC at the same time every day?
- A. Yes
 - B. No
 - C. I do not know
13. What should I do if I forget to take my DOAC?
- A. I should ask my doctor, nurse, or pharmacist, or read the leaflet that comes with my DOAC
 - B. I should always skip that dose and wait until the next dose
 - C. I should always take a double dose at the next dose time
 - D. I do not know

Table 2-6: Version 2.0 of the Questionnaire for PE patients

Questionnaire

Please choose **ONE** correct answer per question by circling the option (A, B, C, or D).

If you do not know the correct answer, please choose "I do not know".

Questions about Pulmonary Embolism (PE) in general

1. **What is meant by PE?**
 - A. A condition that makes the blood less able to clot, causing easy bleeding
 - B. A block in a blood vessel in the lungs, most commonly by a blood clot**
 - C. A condition where there is not enough iron in the blood, causing tiredness
 - D. I do not know
2. **Will I always feel symptoms with PE?**
 - A. Yes
 - B. No**
 - C. I do not know
3. **DOACs can:**
 - A. Ensure you will never have a blood clot again
 - B. Make a blood clot much less likely to happen**
 - C. Lower your blood pressure
 - D. I do not know
4. **Being overweight:**
 - A. Can increase the risk of PE**
 - B. Has no effect on PE
 - C. Protects against PE
 - D. I do not know
5. **What factors can increase the risk of PE?**
 - A. Eating a Mediterranean diet of oily fish, vegetables, fruit etc.
 - B. Smoking, immobility, and taking combined oral contraceptive pills**
 - C. Moderate exercise or physical activity
 - D. I do not know

Questions about Direct Oral Anticoagulants (DOACs)

6. **When should I take my DOAC?**
- A. I should only take my DOAC if I have a stroke
 - B. I should only take my DOAC when I feel signs of PE
 - C. I should always take my DOAC as prescribed, even if I do not feel symptoms of PE**
 - D. I do not know
7. **Possible side effects of DOACs are:**
- A. Headaches and dizziness
 - B. Low blood pressure
 - C. Easy bruising or bleeding**
 - D. I do not know
8. **Which painkillers are safe to take with DOACs?**
- A. Any painkiller
 - B. Painkillers containing paracetamol**
 - C. One of the following anti-inflammatory painkillers: Aspirin or ibuprofen
 - D. I do not know
9. **What should I do if I often have minor nose bleeds (that stop on their own)?**
- A. I should stop taking my DOAC
 - B. I should contact my doctor while I keep taking my DOAC**
 - C. I should go to the hospital
 - D. I do not know
10. **What should I do if I experience a major bleed e.g. coughing up blood?**
- A. I should stop taking my DOAC
 - B. I should wait for a day to see if it stops
 - C. I should call my doctor straight away**
 - D. I do not know
11. **What if I need an operation?**
- A. I should keep taking my DOAC
 - B. I should discuss my DOAC with the doctor**
 - C. I should stop taking my DOAC one week before the operation
 - D. I do not know

12. **Is it important to take my DOAC at the same time every day?**
- A. Yes
 - B. No
 - C. I do not know
13. **What should I do if I forget to take my DOAC?**
- A. I should ask my doctor, nurse, or pharmacist, or read the leaflet that comes with my DOAC
 - B. I should always skip that dose and wait until the next dose
 - C. I should always take a double dose at the next dose time
 - D. I do not know

Table 2-7: Version 3.0 of the Questionnaire for AF Patients

Questionnaire

Please choose **ONE** correct answer per question by **circling the option (A, B, C, or D)**.

If you do not know the correct answer, please choose "I do not know".

Questions about Atrial Fibrillation (AFib) in general

1. What is meant by AFib?

- A. A condition where the heart beats irregularly and often faster than normal**
- B. A heart muscle disease where the heart is too weak to pump enough blood around the body
- C. A disease of the blood causing blood clots in the heart
- D. I do not know

2. Will I always feel symptoms with AFib?

- A. Yes
- B. No**
- C. I do not know

3. What can I do to detect AFib?

- A. Nothing, AFib is very hard to detect and only a doctor can recognise it
- B. I could possibly detect AFib by taking my pulse twice a day for two weeks and noting the result, or using a device such as a smart watch**
- C. By doing an AFib urine test which I can get at the pharmacy
- D. I do not know

4. What are the possible effects of AFib?

- A. It has no harmful effects
- B. It can cause blood clots which can then cause a stroke**
- C. It can cause high blood pressure, and the body will retain fluid
- D. I do not know

5. Direct Oral Anticoagulants (DOACs) can:

- A. Stop AFib, so that it will never come back
- B. Mostly stop AFib: It will only occur sometimes
- C. Reduce the risk of serious stroke in AFib**
- D. I do not know

6. Should I go to the doctor each time I feel AFib?

- A. Yes
- B. No**
- C. I do not know

7. **Being overweight:**
- A. **Can increase the risk of AFib**
 - B. Has no effect on AFib
 - C. Protects against AFib
 - D. I do not know
8. **What factors can increase the risk of AFib?**
- A. Eating a Mediterranean diet of oily fish, vegetables, fruit etc.
 - B. **Smoking, too much alcohol intake, and having high blood pressure**
 - C. Moderate exercise or physical activity
 - D. I do not know
9. **Why are anticoagulants (blood thinners) often prescribed for patients with AFib?**
- A. To prevent fluid retention
 - B. **To reduce the risk of stroke**
 - C. To lower blood pressure
 - D. I do not know

Questions about Direct Oral Anticoagulants (DOACs)

10. **When should I take my DOAC?**
- A. I should only take my DOAC if I have a stroke
 - B. I should only take my DOAC when I feel signs of AFib
 - C. **I should always take my DOAC as prescribed, even if I do not feel symptoms of AFib**
 - D. I do not know
11. **Possible side effects of DOACs are:**
- A. Headaches and dizziness
 - B. Low blood pressure
 - C. **Easy bruising or bleeding**
 - D. I do not know
12. **Which painkillers are safe to take with DOACs?**
- A. Any painkiller
 - B. **Painkillers containing paracetamol**
 - C. One of the following anti-inflammatory painkillers: Aspirin or ibuprofen
 - D. I do not know
13. **What should I do if I often have minor nose bleeds (that stop on their own)?**
- A. I should stop taking my DOAC
 - B. **I should contact my doctor while I keep taking my DOAC**
 - C. I should go to the hospital
 - D. I do not know

14. What should I do if I experience a major bleed, e.g. coughing up blood?

- A. I should stop taking my DOAC
- B. I should wait for a day to see if it stops
- C. I should call my doctor straight away**
- D. I do not know

15. What if I need an operation?

- A. I should keep taking my DOAC
- B. I should discuss my DOAC with the doctor**
- C. I should stop taking my DOAC one week before the operation
- D. I do not know

16. Is it important to take my DOAC at the same time every day?

- A. Yes**
- B. No
- C. I do not know

17. What should I do if I forget to take my DOAC?

- A. I should ask my doctor, nurse or pharmacist, or read the leaflet that comes with my DOAC**
- B. I should always skip that dose and wait until the next dose
- C. I should always take a double dose at the next dose time
- D. I do not know

About you

18. My age is: _____ years

19. My gender is:

- A. Male
- B. Female
- C. Other: _____

20. The highest level of education I have reached is:

- A. Primary school
- B. Secondary school
- C. Third level (undergraduate qualification)
- D. Third level (postgraduate qualification)

21. Besides my DOAC, I take the following other prescribed medicine(s):

(Please list, if any, or otherwise state 'None'.)

3. Counselling Aid for Pharmacists

Table 3-1: Counselling Aid for Pharmacists

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Drug Action	Factor Xa directed inhibitor	Direct thrombin inhibitor	Factor Xa direct inhibitor	Factor Xa direct inhibitor
Indications and Dosing Instructions	- Twice daily, 12 hours apart, with or without food - Long term for NVAf - VTE: 10mg BD for 7 days followed by 5mg BD for at least three months, treatment duration in individualised. - Reduced dose of 2.5mg BD in patients with ≥ 2 of the following characteristics: age ≥ 80 years; body weight ≤ 60kg; serum creatinine ≥ 1.5mg/dL	- Prophylaxis of VTE following total knee replacement surgery: Once daily (220mg for 10 days) - Treatment of DVT: Twice daily (110-150mg bd) - Prophylaxis of stroke in NVAf: twice daily (110-150mg bd) - Taken with or without food with a glass of water - Dose reduction in renal impairment and in patients ≥ 75	- Once daily with/without food 60mg: recommended daily dose 30mg: moderate renal impairment < 60kg and/or concomitant use of P-gp inhibitor - Long term for NVAF - For VTE, after 5 days of parenteral anticoagulant	- Once daily with food - Prevention of stroke and systemic embolism - Treatment and prevention of recurrent DVT and PE
Interactions	Anticoagulants, antiplatelets e.g., NSAIDs, thrombolytics, SSRIs, SNRIs,	Anticoagulants, antiplatelets e.g., NSAIDs, thrombolytics, SSRIs, SNRIs, strong	Anticoagulants, antiplatelets e.g., NSAIDs, thrombolytics, SSRIs, SNRIs, strong	Anticoagulants, antiplatelets e.g., NSAIDs, thrombolytics, SSRIs, SNRIs,

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
	strong inhibitors of CYP3A4 and P-gp, e.g., ketoconazole, HIV protease inhibitors; inducers of CYP3A4 and P-gp e.g., rifampicin, phenytoin, carbamazepine, St John's Wort	inhibitors of CYP3A4 and P-gp, e.g., ketoconazole, HIV protease inhibitors; inducers of CYP3A4 and P-gp e.g., rifampicin, phenytoin, carbamazepine, phenobarbital, St. John's Wort, pantoprazole, or ranitidine (substances influencing gastric pH)	inhibitors of CYP3A4 and P-gp, e.g., ketoconazole, HIV protease inhibitors; inducers of CYP3A4 and P-gp e.g., rifampicin, phenytoin, carbamazepine, phenobarbital, St. John's Wort.	strong inhibitors of CYP3A4 and P-gp, e.g., ketoconazole, HIV protease inhibitors; inducers of CYP3A4 and P-gp e.g., rifampicin, phenytoin, carbamazepine, phenobarbital, St. John's Wort
Common Side Effects	Bleeding, bruising, and swelling, nausea, anaemia, diarrhoea or constipation, cough	Bleeding and bruising, anaemia, gastrointestinal haemorrhage, abdominal pain, diarrhoea, dyspepsia, nausea	Bleeding; anaemia, haemorrhage, nausea, skin reactions, dizziness, headache, blood test abnormalities	Bleeding, anaemia, swelling and pain in limbs, fever, indigestion, constipation or diarrhoea, dizziness, tiredness, rash
Patient Alert Card	All patients taking apixaban should carry an alert card in their wallet at all times in case of an emergency due to increased risk of bleeding.	All patients taking dabigatran should carry an alert card in their wallet at all times in case of an emergency due to increased risk of bleeding.	All patients taking edoxaban should carry an alert card in their wallet at all times in case of an emergency due to increased risk of bleeding.	All patients taking rivaroxaban should carry an alert card in their wallet at all times in case of an emergency due to increased risk of bleeding.
When to Contact a Hcp	If any of the side effects mentioned are experienced, before taking other medication, before having a medical procedure done, if a dose	If any of the side effects mentioned are experienced, before taking other medication, before having a medical procedure done, if a dose has been missed	If any of the side effects mentioned are experienced, before taking other medication, before having a medical procedure done, if a dose has been missed	If any of the side effects mentioned are experienced, before taking other medication, before having a medical procedure done, if a dose

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
	has been missed			has been missed
Renal/Hepatic Impairment	Reduced dose of 2.5mg BD in patients with ≥ 2 of the following characteristics: age ≥ 80 years; body weight ≤ 60 kg; serum creatinine ≥ 1.5 mg/dL. Not recommended for use in patients with severe hepatic impairment; use with caution in patient with mild or moderate hepatic impairment.	Renal impairment: dabigatran is contraindicated in patients with severe renal impairment ($\text{CrCL} < 30 \text{ mL/min}$). A dose reduction is recommended in patients with moderate renal impairment in cases with a high bleeding risk. The use of dabigatran is not recommended in those with hepatic impairment	Reduce dose to 30mg if CrCl is 15-50ml/min; not recommended if $\text{CrCl} < 15 \text{ mL/min}$. Contraindicated in hepatic disease; caution in mild-moderate hepatic impairment	Renal impairment: Reduced dose of 15mg OD. For DVT/PE treatment and prevention, 15mg BD 3/52 then 15mg OD; not Recommended if $\text{CrCl} < 15 \text{ mL/min}$. Contraindicated in hepatic disease.
Missed/Extra Doses	If a dose is missed, take as soon as possible and then take the next dose at the usual time. Overdose can lead to haemorrhage; seek medical advice if an extra dose(s) is taken. A reversal agent is available.	A forgotten dabigatran dose may still be taken up to 6 hours prior to the next scheduled dose. From 6 hours prior to the next scheduled dose on, the missed dose should be omitted. No double dose should be taken to make up for missed individual doses.	If a dose is missed, take as soon as possible up to 12 hours after scheduled time; after this, skip the dose and resume as normal the next day. Overdose may lead to haemorrhage; seek medical advice.	Take as soon as possible and then take the next dose at the usual time. If you are taking 15mg BD and forget a dose, you can take 30mg on one day but resume to BD dosing thereafter. Overdose increases risk of bleeding.
Precautions For Use	In patients with increased risk of bleeding; prosthetic heart valve; haemodynamically unstable PE	In patients with an increased risk of bleeding, hepatic impairment, prosthetic heart valve, patients with active cancer,	In patients with a mechanical heart valve, severe liver disease, bleeding disorders, retinopathy, or a recent cranial bleed.	In patients with increased risk of bleeding; renal impairment, prosthetic heart valve; in

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
	patients; patients who require thrombolysis or pulmonary embolectomy; active cancer; renal impairment; hepatic impairment.	patients with myocardial infarction	Not recommended if CrCl >95ml/min. Reduce dose to 30mg in those ≤ 60kg or a high risk of a gastrointestinal bleed.	NVAF who undergo PCI with stent placement; anaesthesia
Contra-Indications	• Antiphospholipid syndrome • Hypersensitivity to the API/excipients • Active bleeding. • Hepatic disease associated with coagulopathy and clinically relevant bleeding risk. • Lesion or condition if considered a significant risk factor for major bleeding. • Concomitant treatment with another anticoagulant • Pregnancy/breast-feeding	• Antiphospholipid syndrome • Hypersensitivity to the API/excipients • Patients with severe renal impairment (CrCL < 30 mL/min) • Active bleeding • Lesion or condition, if considered a significant risk factor for major bleeding. • Concomitant treatment with another anticoagulant • Prosthetic heart valves requiring anticoagulant treatment • Pregnancy/breast feeding • Concomitant treatment with strong P-gp inhibitors	• Antiphospholipid syndrome • Hypersensitivity to the API/excipients • Valvular AF • Active bleeding • Antiphospholipid syndrome • Concomitant treatment with another anticoagulant • Hypersensitivity to the active substance or excipients • Uncontrolled, severe hypertension • Hepatic disease • Pregnancy/breast feeding	• Antiphospholipid syndrome • Hypersensitivity to the API/excipients • Active bleeding • Lesion or condition if considered a significant risk factor for major bleeding. • Concomitant treatment with another anticoagulant. • Hepatic disease • Pregnancy/breast-feeding
Switching	From VKA therapy to	Parenteral anticoagulants to	From Non-VKA to edoxaban,	From VKA to rivaroxaban:

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
	apixaban: discontinue VKA therapy and initiate apixaban when INR < 2; this can be done at the next scheduled dose.	dabigatran: the parenteral anticoagulant should be discontinued, and dabigatran should be started 0-2 hours prior to the time that the next dose of the alternate therapy would be due, or at the time of discontinuation in case of continuous treatment VKA to Pradaxa: The VKA should be stopped. Pradaxa can be given as soon as the INR is < 2.	discontinue the non-VKA and start edoxaban at the time of the next non- VKA dose. From VKA to edoxaban, discontinue the VKA and monitor INR until it is less than/equal to 2.5 then start Lixiana once daily	discontinue VKA therapy and initiate rivaroxaban when INR ≤ 3 in prevention of stroke and systemic embolism and when INR ≤ 2.5 in patients treated for DVT, PE and prevention of recurrence.
Surgery	For procedures with moderate-high risk of bleeding: discontinue apixaban ≥ 48 hours before procedure. For procedures with low risk of bleeding: discontinue apixaban ≥ 24 hours before procedure. Restart apixaban as soon as possible after the procedure. For catheter ablation for AF, apixaban treatment does not need to be interrupted.	If possible, dabigatran should be discontinued at least 24 hours before invasive or surgical procedures. In patients at higher risk of bleeding or in major surgery where complete haemostasis may be required consider stopping dabigatran 2-4 days before surgery.	Discontinue edoxaban at least 24 hours before the procedure. Exercise caution due to increased risk of thrombosis. In the case of an emergency, analysis of bleeding risk should be carried out and weighed against the urgency of the procedure. Restart as soon as haemostasis is achieved.	Stop rivaroxaban at least 24 hours before the procedure. In deciding whether a procedure should be delayed until 24 hours after the last dose of rivaroxaban, the increased risk of bleeding should be weighed against the urgency of intervention. Restart Rivaroxaban as soon as adequate haemostasis is established.