USE OF WARFARIN AND NOVEL ORAL ANTICOAGULANTS (NOACS)

Submitted in partial fulfilment
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Degree of Master of Pharmacy

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Dedication

This research is dedicated to all those whom for some reason or another have decided to abandon their studies.

There comes a time where we have to take a step back. But, it does not always have to remain that way. I have been *there*, but I am **here** now.

And you can be too. Take your time, never say never and it is never too late. You have the potential and you can make a difference. Be that difference.

And if it is not for you, that is okay too.

But if it is, may this work be an inspiration to us all. Let it be the spark to help us make that leap, for us, for all those who need our help. Let us empower and help one other to move from *there* to **here.**

Abstract

Warfarin is a commonly prescribed oral anticoagulant. It has a narrow therapeutic window and requires frequent International Normalised Ratio (INR) monitoring. Warfarin doses vary according to the INR. NOACs include apixaban, dabigatran and rivaroxaban. NOACs have a predictable anticoagulant effect and therefore doses are fixed. NOACs do not require INR monitoring. NOACs have less food and drug interactions than warfarin. The main limitation of NOACs over warfarin is their high cost. Not all warfarin patients should be switched to a NOAC. Patients who are stable on warfarin and patients with a mechanical valve or valvular atrial fibrillation (AF) should not be switched to a NOAC. (Verdecchia *et al.*, 2016)

The aims of this study are to assess the level of knowledge of health care professionals (HCPs) on NOACs and to assess perception of patients on warfarin regarding adherence to treatment, awareness of NOACs and willingness to switch to a NOAC.

The study is set in 8 community pharmacies, conveniently sampled from the different statistical districts. Each pharmacy analysed and identified the amount of warfarin and NOACs patients. The amount of warfarin patients was higher in all 5 districts.

Three questionnaires were formulated and validated; one for general practitioners (GPs), one for pharmacists and one for warfarin patients. A total of 21 GPs, 25 pharmacists and 76 patients were interviewed.

The HCPs highlighted the advantages and disadvantages of both classes of oral anticoagulants. The high cost of NOACs and need to include them in the government's outpatients formulary list were emphasised.

The results from the patients questionnaire showed that the interviewees seem to be well-controlled on warfarin. A few patients experienced adverse drug reactions (ADRs), 2 of which required hospitalisation. The majority of patients know about the availability of NOACs and about the differences from warfarin. Only a minority of patients are willing to switch and pay for NOACs (if suitable for them).

The inclusion of NOACs in the government's outpatient's formulary list will increase accessibility. Nonetheless, the use of warfarin will not stop here. It is of utmost importance to keep on educating patients making use of anticoagulant treatment, particularly warfarin.

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List of Abbreviations

ACC – Anticoagulation Clinic

ACS – Acute Coronary Syndrome

ADRs – Adverse Drug Reactions

AF – Atrial Fibrillation

aPTT – activated Partial Thromboplastin Time

AUDIT – Alcohol Use Disorders Identification Test

CAD – Coronary Artery Disease

CrCl – Creatinine Clearance

DDIs – Drug-drug interactions

DOACs – Direct Oral Anticoagulants

DVT – Deep Vein Thrombosis

ECT – Ecarin Clotting Time

eGFR – estimated Glomerular Filtration Rate

EU – European Union

FDA – Food and Drug Administration

FFP – Fresh Frozen Plasma

FREC – Faculty Research Ethics Committee

FTND – Fagerstrom Test for Nicotine Dependence

GI – Gastrointestinal

GP – General practitioner

HCP – Health Care Professional

INR – International Normalised Ratio

IV – Intravenous

MATE-1 – Multidrug and Toxin Extrusion-1

MDH – Mater Dei Hospital

MHV – Mechanical Heart Valve

MI – Myocardial Infarction

NOACs – Novel Oral Anticoagulants

NVAF – Non-Valvular Atrial Fibrillation

OTC – Over The Counter

PAD – Peripheral Artery Disease

PE – Pulmonary Embolism

P-gp – P-glycoprotein

PK – Pharmacokinetic

POCT – Point-Of-Care Testing

POM – Prescription Only Medicine

POYC – Pharmacy Of Your Choice

PT – Prothrombin Time

REDP – Research Ethics and Data Protection

SE – Systemic Embolism

TIA – Transient Ischaemic Attack

T_{max} – Time to reach peak plasma concentration

UFH – Unfractionated heparin

US – United States

VHD – Valvular Heart Disease

VKA – Vitamin K Antagonist

VTE – Venous Thromboembolism

CHAPTER 1

INTRODUCTION

1.1 Use of anticoagulants

Anticoagulants are drugs that prevent coagulation; the formation of blood clots. They are more commonly known as "blood thinners" with lay persons. A blood clot can limit blood flow through blood vessels resulting in hypoxia to the affected organ. This will limit the organ's ability to function properly. Complications that may arise include deep vein thrombosis (DVT), pulmonary embolism (PE), stroke or transient ischaemic attack (TIA) and myocardial infarction (MI).

Anticoagulants are prescribed both for prophylaxis and treatment of blood clots. Patients warranting anticoagulant treatment include those at an increased risk or with a past history of a blood clot. Patients with atrial fibrillation (AF) and those who have recently undergone surgery, particularly hip and knee replacements, are at a higher risk due to immobility. Anticoagulants may be administered orally (oral anticoagulants) or parenterally eg. heparin.[1] For the purpose of this research, oral anticoagulants only will be discussed.

1.2 Oral anticoagulants available

Warfarin, a coumarin, is the most commonly used oral anticoagulant internationally and locally. Warfarin was authorised as an anticoagulant for human use in 1954 (Pirmohamed, 2006). Warfarin is a vitamin K antagonist (VKA), leaving vitamin K in the body inactivated. Coagulation factors II, VII, IX and X and coagulation regulatory factors,

[1] Anticoagulant medicines [Internet]. UK: NHS; 2021 [cited 2021 Aug 6]. Available from: https://www.nhs.uk/conditions/anticoagulants/.

proteins C and S are vitamin K dependent. The lack of activated vitamin K results in the reduction of the synthesis of the aforementioned clotting factors.[2]

Novel oral anticoagulants (NOACs) are non-VKA oral anticoagulants, and include apixaban, dabigatran, edoxaban and rivaroxaban. In 2010, dabigatran was the first NOAC approved by the US Food and Drug Administration (FDA). It was then followed by rivaroxaban, apixaban and edoxaban. NOACs are also known as direct oral anticoagulants (DOACs) as they target specific clotting factors in the coagulation cascade. Dabigatran is a direct thrombin (factor IIa) inhibitor and apixaban, edoxaban and rivaroxaban are direct factor Xa inhibitors. (Chen *et al.*, 2020)

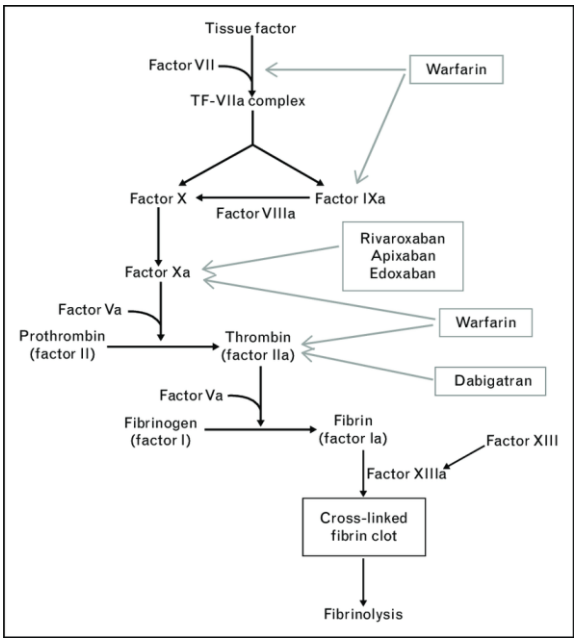

Figure 1.1: Different oral anticoagulants and their effects on the coagulation cascade (adopted from Grottke *et al*.,2015)

[2] Warfarin [Internet]. Bethesda, MD: NCBI; 2021 [cited 2021 Jul 3]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470313/.

1.2.1 Warfarin

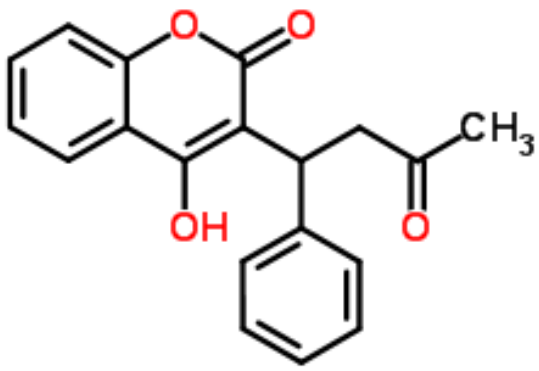

Figure 1.2: Molecular structure of warfarin[3]

Warfarin is a racemic mixture of R and S enantiomers, each metabolised through individual pathways. The S-enantiomer is 3 to 5 times more potent than the R-enantiomer. Warfarin is indicated for the prophylaxis and treatment of venous thrombosis and PE. Warfarin is also used for the treatment and prevention of thromboembolic complications from AF or cardiac valve replacement. Warfarin reduces the risk of mortality, recurrent MI and thromboembolic post-MI. Warfarin is also used off-label for the secondary prevention of recurrent stroke and TIAs.

Warfarin is to be administered once daily, ideally at the same time each day. Onset of action of the drug varies from 24 to 72 hours and peak therapeutic effect is achieved within 5 to 7 days. Initially, warfarin treatment needs to be bridged with heparin

[3] Adopted from Warfarin [Internet]. Royal Society of Chemistry: ChemSpider; [cited 2021 Jul 3]. Available from: http://www.chemspider.com/Chemical-Structure.10442445.html

(unfractionated or low-molecular-weight) treatment. The half-life varies from 20 to 60 hours and is interpatient variable. Warfarin is hepatically metabolised, mainly via the CYP2C9 enzyme and primarily renally excreted.[2]

1.2.2 NOACs

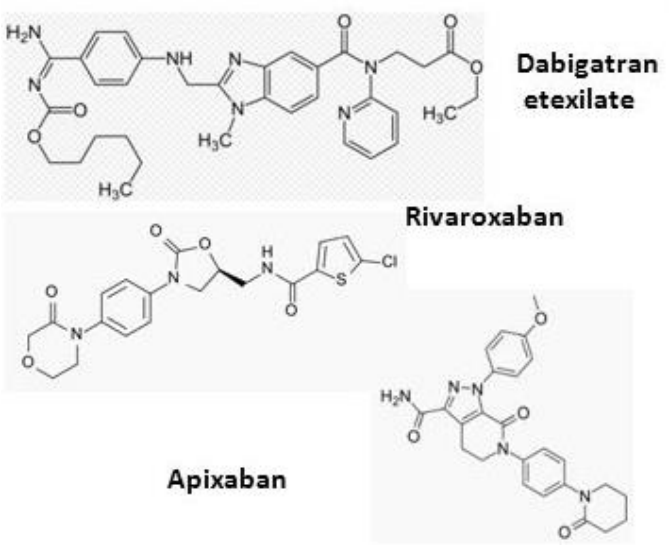

Figure 1.3: Molecular structures of NOACs[4]

Apixaban, dabigatran and rivaroxaban are indicated for the prophylaxis of venous thromboembolism (VTE) following total hip and knee replacement, prophylaxis of recurrent DVT and PE and treatment of DVT and PE. Apixaban, dabigatran and rivaroxaban are also indicated for the prevention of stroke and systemic embolism (SE) in non-valvular AF (NVAF) (with one or more risk factors). Rivaroxaban alone is indicated for the prophylaxis of atherothrombotic events following an acute coronary syndrome (ACS) with elevated cardiac biomarkers (in combination with aspirin alone or aspirin and clopidogrel). Rivaroxaban is also used as prophylaxis of atherothrombotic

[4] Adapted from New Oral Anticoagulants; slide 32 [Internet]. SlidePlayer; 2015 [cited 2021 Jul 7]. Available from: https://slideplayer.com/slide/10228499/.

events in patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events (in combination with aspirin).

Dabigatran etexilate is a prodrug and does not exert any pharmacological activity. It is rapidly absorbed and converted to dabigatran in the liver and plasma. Apixaban is given as a twice daily regimen. Dabigatran and rivaroxaban are to be administered once or twice daily, depending on the indication it has been prescribed for. (BNF, 2021).

	Apixaban	Dabigatran	Rivaroxaban
T_{max} (hours)	1 – 4	1 – 3	2 – 4
Half-life (hours)	8 – 15	11 – 14	5 – 13
Metabolism via CYP450 (%)	< 32	< 2	57
Excretion	25 % urine, 75 % faeces	80 % urine, 20 % faeces	70 % urine, 30 % faeces

T_{max} = time to reach peak plasma concentration

Table 1.1: Pharmacology of NOACs
(Adapted from Gelosa et al., 2018)

1.3 Comparing and contrasting the different oral anticoagulants

Warfarin and NOACs differ in their mode of actions and pharmacokinetic profiles. There are differences in their indications, dosing and need for monitoring, contraindications, drug and food interactions and adverse effects. These are further discussed in the following sections.

1.3.1 Indications

As briefly mentioned in section 1.2 above, both warfarin and NOACs are approved for use in NVAF. Studies have shown that NOACs have similar safety and efficacy profiles to warfarin when used for NVAF. Three studies, one for each of the NOACs were conducted; ARISTOTLE for apixaban, RE-LY for dabigatran and ROCKET-AF for rivaroxaban. In all three studies the respective NOAC was compared to warfarin (Tendera *et al.*, 2012). Different patients were included in the different studies. All three studies excluded different sub-groups that had a particular valvular disease (Ezekowitz and Kent, 2013).

During ARISTOTLE, apixaban was found to be superior to warfarin in reducing stroke (both ischaemic and haemorrhagic) and major bleeding. Patients, to whom apixaban was administered, had lower rates of intracranial bleeding and a statistically significant decreased mortality rate. (Granger *et al.*, 2011; Pokorney *et al.*, 2013)

RE-LY demonstrated that 150 mg dabigatran twice daily was superior to warfarin in the prophylaxis of stroke and SE in patients with NVAF. Incidents of ischaemic and haemorrhagic strokes and intracranial bleeding were lower. Rates of major bleeding were similar. There was an increase in GI bleeding. A small increased risk of MI was seen with

dabigatran 150 mg twice daily when compared to warfarin, however, this was not statistically significant. (Connolly *et al.*, 2009; Pokorney *et al.*, 2013)

The patients included in ROCKET-AF were at a higher risk of developing a thromboembolic event. With respect to major bleeding, rivaroxaban was non-inferior to warfarin. Patients receiving rivaroxaban were at a lower risk of haemorrhagic stroke and intracranial bleeding. A small decreased risk of MI was observed with rivaroxaban, but this was not statistically significant. (Patel *et al.*, 2011; Pokorney *et al.*, 2013)

	ARISTOTLE	RE-LY	ROCKET-AF
Stroke and SE	0.79	0.65	0.88
Ischaemic or unspecified stroke	0.92	0.76	0.91
Haemorrhagic stroke	0.51	0.26	0.59
MI	0.88	1.27	0.81
All-cause mortality	0.89	0.88	0.85
Major bleeding	0.69	0.93	1.04
GI bleeding	0.89	1.50	1.47
Intracranial bleeding	0.42	0.40	0.67

A ratio higher than 1 favors warfarin.

Table 1.2: Average hazard ratios for NOACs compared with warfarin
(Adapted from Pokorney *et al.*, 2013)

Warfarin is also indicated in cases where there have been a valve replacement. To date, NOACs have not been approved for such indication yet as data is still limited. In the analysis carried out by de Souza Lima Bitar *et al.,* 2019, six randomised controlled trials (RCTs), with a total of 13,553 patients were chosen. These studies compared the use of NOACs with that of warfarin in patients with AF and valvular heart disease (VHD), including biological and mechanical heart valves (MHV). NOACs were found to be more effective than warfarin with a significantly lowered risk of intracranial haemorrhage, stroke and SE in patients with VHD and MHV. Also, the risk of major bleeding was lowered.

In another study, Briasoulis *et al.,* 2018 examined a sample of patients with AF; 5,871 with VHD (excluding prosthetic valves) and 40,221 without VHD and AF. Patients were taking either dabigatran, rivaroxaban or warfarin as anticoagulant. Dabigatran and rivaroxaban were associated with a significant lower risk of both all-cause mortality and non-gastrointestinal (GI) bleeding when compared to warfarin in patients with or without VHD with AF. There was no difference between the three oral anticoagulants in the rates of ischaemic stroke in patients with VHD. Rivaroxaban was found to have lower stroke rates than warfarin in patients without VHD. Higher GI bleeding rates were observed with rivaroxaban when compared with both dabigatran and warfarin in patients without VHD.

1.3.2 Dosing and monitoring

Locally, warfarin is available in 3 colour-coded doses as per the below figure.

Figure 1.4: Warfarin doses available locally [5]

Apixaban, marketed as Eliquis® is available in 2.5 and 5 mg tablets. Dabigatran is available as Pradaxa® 75, 110 and 150 mg capsules. Rivaroxaban is available as Xarelto® 2.5, 10, 15 and 20 mg tablets

Warfarin is a drug with a narrow therapeutic window. Therapeutic efficacy is inter- and intra-patient variable. Warfarin patients require frequent monitoring to ensure safety and efficacy. The blood tests done do not represent the plasma levels of warfarin but the time taken for blood to clot; the prothrombin time (PT), reported as International Normalised Ratio (INR). INR is a standardised system of expressing the PT. This enables comparison of tests from different laboratories. This ratio compares the time taken for the patient's blood to form a clot with the time taken for untreated blood to form a clot. A healthy subject should have an INR level of 1. Patients on anticoagulants have a target INR of 2 to 3 which may vary slightly according to the condition being treated. Patients with MHVs

[5] Adopted from What is Warfarin? [Internet]. UK: Whittington Health NHS Trust; [cited 2021 Jul 15]. Available from: https://www.whittington.nhs.uk/default.asp?c=7458.

may have an INR target ranging from 2.5 to 3.5 due to the higher risk of thromboembolism. (Kuruvilla *et al.*, 2001)

Frequency of INR monitoring depends on patient's stability and compliance to treatment. Lack of monitoring and / or non-compliance may result in sub- or supratherapeutic levels. Patients may need to be admitted to hospital for closer monitoring. This increases healthcare burden.

Figure 1.5: INR scale[6]

If needed, dose alterations, will be made according to the INR results. There are no particular preparations needed for the INR test. INR tests are usually done in the morning. The clinic then, contacts the patient and advises the dose to be taken until the next INR appointment. It is suggested that warfarin dose is taken in the evening. This shortens the response time for making a dose change, if needed.

NOACs have a more predictable effect than warfarin, therefore there is no need for routine monitoring and / or dose alterations. Drug concentrations can be measured but there is no existing correlation between drug concentrations and risk of bleeding (Fenger-Eriksen *et al.*, 2014). This especially applies to special populations eg. elderly and renally

[6] Warfarin and INR [Internet]. New Zealand: Health Navigator; 2021 [cited 2021 Jul 17]. Available from: https://www.healthnavigator.org.nz/medicines/w/warfarin-and-inr/.

impaired. Eikelboom *et al.*, 2017 states that "unmonitored NOAC therapy is at least as effective and safe as monitored warfarin, with lower rates of intracranial haemorrhage and reduced mortality."

CoaguChek®

The traditional way of INR testing is via a sample of venous blood. A new, modern way of testing for INR exists. The sample is a drop of capillary, whole blood through the use of a fingerstick. This makes the test less invasive. The system is fast and results are precise and reliable. This allows for more rapid instructions regarding dose changes (if needed). The CoaguChek® system is a point-of-care testing (POCT) developed by Roche diagnostics. The system is able to measure INR ranging from 0.8 to 8. CoaguChek® allows self-monitoring. Heneghan *et al.*, 2006, states that patients who are able to self-adjust therapy (apart from self-monitoring) have less thromboembolic event and mortality.

Figure 1.6: CoaguChek® XS[7]

[7] Reproduced from CoaguChek® XS system [Internet]. Roche Diagnostics [cited 2021 Aug 10]. Available from: https://diagnostics.roche.com/global/en/products/instruments/coaguchek-xs.html#productInfo.

The test strips contain chemicals that when in contact with the blood sample, lead to an electric current within the strip. When the system determines that the blood has clotted, the process stops. The blood-clotting time is determined and displayed as INR.[8]

1.3.3 Cautions and Contraindications

Cautions for warfarin use include bacterial endocarditis, conditions which increase risk of bleeding, history of GI bleeding or peptic ulcer, hyper and hypothyroidism, postpartum, recent ischaemic stroke or surgery and uncontrolled hypertension.

Apixaban, dabigatran and rivaroxaban should be used with caution in anaesthesia with postoperative indwelling epidural catheter and in cases where there is risk of bleeding or bleeding disorders. Apixaban and rivaroxaban are to be used with caution in patients with prosthetic heart valve due to unestablished efficacy. Dabigatran is cautioned in patients with bacterial endocarditis, body weight less than 50 kg, elderly, thrombocytopenia and GI problems and patients who had had a recent biopsy or major trauma. Rivaroxaban should also be used with caution in bronchiectasis, elderly, severe hypertension and vascular retinopathy. Rivaroxaban should not replace unfractionated heparin (UFH) in PE in patients with haemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.

[8] CoaguChek XS System [Internet]. CentraCare Laboratory Services; 2017 [cited 2021 Aug 10]. Available from: https://www.centracare.com/documents/CoaguChekXSSystem.pdf.

Table 1.3 below represents a list of contraindications for the different oral anticoagulants.

Warfarin	Apixaban	Dabigatran	Rivaroxaban
Within 48 hours of postpartum	Risk factors for major bleeding		
Haemorrhagic stroke	Antiphospholipid syndrome		
Active, clinically significant bleeding			
Pregnancy (teratogenic)	Pregnancy (no information)	Pregnancy (toxicity in animal studies)	
Avoid in severe hepatic impairment	Severe hepatic impairment or impairment associated with bleeding risk	Severe hepatic impairment, liver enzymes 2 times upper limit (no information)	Hepatic disease with coagulopathy or bleeding risk
	CrCl < 15 mL / minute	CrCl < 30 mL / minute	CrCl < 15 mL / minute
	Breastfeeding (present in animal studies)	Vascular aneurysm	
		Malignant neoplasms at high risk of bleeding	

		Breastfeeding (no information)	Breastfeeding (present in animal studies)
		Oesophageal varices	
		Recent brain / ophthalmic / spine surgery	
		Recent GI ulcer	
		Recent intracranial haemorrhage	
		Prosthetic heart valve	Previous stroke / TIA if used following ACS
			Previous stroke if used after CAD or symptomatic PAD

CrCl = Creatinine Clearance, PAD = Peripheral Artery Disease

Table 1.3: Contraindications to warfarin and NOACs
(Table formulated from data given in BNF, 2021)

1.3.4 Drug-drug interactions (DDIs)

The main DDIs affecting warfarin's pharmacokinetic (PK) profile are those drugs competing for plasme protein-binding sites and those inhibiting and inducing CYP enzymes responsible for warfarin's metabolism. CYP2C9, 1A2 and / or 3A4 inhibitors result in a prolonged anticoagulant effect, therefore increasing the risk of bleeding. On the other hand inducers of the mentioned enzymes will decrease warfarin's effects by increasing its metabolism and clearance.

Cytochrome P450	Inhibitors	Inducers
CYP2C9	amiodarone, fluconazole, fluvoxamine, isoniazid, miconazole, voriconazole	rifampicin
CYP1A2	amiodarone, ciprofloxacin, fluvoxamine, miconazole, propafenone, propranolol, ticlopidine, voriconazole	
CYP3A4	amiodarone, cilostazol, clofibrate, diltiazem, dronedarone, erythromycin, fenofibrate, fluconazole, fluoxetine, fluvoxamine, isoniazid, propafenone, voriconazole	rifampicin

Table 1.4: Clinically relevant interactions with warfarin
(Adapted from Gelosa *et al.*, 2018; Steffel *et al.*, 2018)

Apixaban is eliminated via different pathways, including metabolism by CYP enzymes, mainly CYP3A4. Apixaban may interact with P-glycoprotein (P-gp) substrates and / or modulators of CYP450. Co-administration of apixaban with azole antifungals, clopidogrel, cobicistat, enoxaparin, ketoconazole, levetiracetam, oxcarbazepine, prasugrel and topiramate is not tolerated. Dose adjustments of macrolides (clarithromycin

and erythromycin) should be considered when co-administering with apixaban. Caution should be exercised when co-administering apixaban with aspirin, carbamazepine, naproxen, phenobarbital, phenytoin, rifampicin and St. John's wort.

Dabigatran is a substrate of P-gp and renal multidrug and toxin extrusion-1 transporters (MATE-1), as it is mainly eliminated renally. Dronedarone increase Ecarin clotting time (ECT) % and activated partial thromboplastin time (aPTT) % and co-administration with dabigatran is contraindicated. Co-administering dabigatran and ketoconazole is also contraindicated. Use of statins, other than simvastatin or lovastatin should be considered. Co-administration of dabigatran with carbamazepine, enoxaparin, phenobarbital, phenytoin, rifampicin and St. John's wort should be avoided. Close clinical monitoring is recommended when co-administering dabigatran with amiodarone, clarithromycin, quinidine and verapamil. Caution should be exercised when co-administering dabigatran with clopidogrel. Cobicistat increases PT.

Interactions of rivaroxaban are related to CYP3A4 and P-gp. Co-administration of rivaroxaban with azole antifungals, carbamazepine, conivaptan, enoxaparin, phenobarbital, phenytoin, rifabutin, rifampicin, rifampetine, ritonavir, St.John's wort and warfarin should be avoided. There is limited clinical data on concomitant use of rivaroxaban with dronedarone. Co-administration should be avoided. Caution is recommended with the concomitant use of rivaroxaban with aspirin and clopidogrel.
(Gelosa *et al.,* 2018, Li *et al.,* 2020)

1.3.5 Adverse effects

If anticoagulation is subtherapeutic (low INR if taking warfarin), risk of stroke is increased. Supratherapeutic effects may give rise to bleeding events including epistaxis and blood in stools (high INR if taking warfarin).

Patients with AF should be assessed for the risk of stroke using the CHA_2DS_2-VASc score. Males and females having a score of 0 and 1 respectively are identified as low risk patients and therefore do not require any anticoagulant. The HAS-BLED score assesses the risk of major bleeding a patient has while taking an anticoagulant. A score of 3 or higher is considered as high and should be indicative of the need for close monitoring. In the majority of AF patients, the risk of stroke outweighs the risk of bleeding. The HAS-BLED score should be used as an aid to minimise and control risk factors that may lead to bleeding events eg. blood pressure control. (Lip, 2012; Steinberg *et al.*, 2015, Šinigoj *et al.*, 2020)

CHA_2DS_2-VASc	Score	HAS-BLED	Score
Congestive heart failure/LV dysfunction	1	Hypertension i.e. uncontrolled BP	1
Hypertension	1	Abnormal renal/liver function	1 or 2
Aged ≥75 years	2	Stroke	1
Diabetes mellitus	1	Bleeding tendency or predisposition	1
Stroke/TIA/TE	2	Labile INR	1
Vascular disease [prior MI, PAD, or aortic plaque]	1	Age (e.g. >65)	1
Aged 65-74 years	1	Drugs (e.g. concomitant aspirin or NSAIDSs) or alcohol	1
Sex category [i.e. female gender]	1		
Maximum score	**9**		**9**

Figure 1.7: CHA_2DS_2-VASc and HAS-BLED scores

(Reproduced from Lip, 2012)

The ATRIA and ORBIT scores are other assessment scores for bleeding risk. Patients scoring 5 and 4 or higher for ATRIA and ORBIT respectively, are considered at a high risk.

ATRIA	Score	ORBIT	Score
Anaemia	3	Anaemia	1
Severe renal disease (eGFR < 30 mL / min / 1.73 m^2)	3	Insufficient kidney function (eGFR < 60 mL / min / 1.73 m^2)	1
Age ≥ 75 years	2	Age > 74 years	1
Prior bleeding	1	Prior bleeding	2
Hypertension	1	Treatment with an antiplatelet	2
Maximum score	10	Maximum score	7

eGFR = estimated glomerular filtration rate

Table 1.5: ATRIA and ORBIT scores

(Table formulated from data given in Senoo *et al.*, 2016)

The study performed by Senoo *et al,*. 2016 compared the predictive abilities of the HAS-BLED, ATRIA and ORBIT scores. All 3 scores were found to be fairly predictive with the HAS-BLED being better.

Drug reversal

	Warfarin	Apixaban / Rivaroxaban	Dabigatran
Reversal agent	Phytomenadione (vitamin K)	Andexanet alfa (Ondexxya®)	Idarucizumab (Praxbind®)

Table 1.6: Reversal agents for the different oral anticoagulants
(Table formulated from data given in BNF, 2021)

Phytomenadione may be administered by slow intravenous (IV) injection or orally (unlicensed). It is indicated in patients on warfarin experiencing major bleeding (in combination with dried prothrombin complex or fresh frozen plasma). It is also indicated in warfarin patients with an INR of 5 – 8 with minor bleeding and INR greater than 8 with or without minor bleeding. Vitamin K is used for the reversal of anticoagulation prior to elective or emergency surgery.

DOAC-associated bleeding should first be treated with supportive measures. Such measures include discontinuing the DOAC and other agents that may affect haemostasis eg. aspirin, compression at bleeding site, volume resuscitation and transfusion support. Where mucosal bleeding is present eg. epistaxis or uterine bleeding, an antifibrinolytic may be used. Oral activated charcoal may help eliminate any unabsorbed DOAC from the GI tract. If patient is unresponsive to these measures, reversal agents should be used. (Cuker *et al.,* 2019)

Andexanet alfa is a recombinant human factor X_a which binds specifically to apixaban and rivaroxaban, to reverse their anticoagulant effects. It is administered as an IV infusion. It should be limited to life-threatening or uncontrolled bleeding.

Idarucizumab is a human monoclonal antibody fragment that binds specifically to dabigatran and its metabolites to reverse its anticoagulant effects. Administration is via an IV injection or infusion. It is indicated for rapid reversal for emergency procedures and in life-threatening or uncontrolled bleeding.

1.3.6 Lifestyle

Being a VKA, warfarin's effects, are reduced by vitamin K; including that found in foods, supplements, enteral feeds, green leafy vegetables or green tea. Green leafy vegetables include kale, spinach, brussel sprouts, broccoli and cabbage[9]. Heran *et al.,* 2016 discusses the fact that taking warfarin in the morning may be more benedicial, since breakfast is typically less rich in vitamin K. This may lead to greater stability in anticoagulant effect.

[9] Warfarin, your diet, and vitamin K foods [Internet]. Iowa City, IA: University of Iowa Hospitals & Clinics; 2017 [cited 2021 Aug 10]. Available from: https://uihc.org/health-topics/warfarin-your-diet-and-vitamin-k-foods.

Food (no salt added)	Serving size	Vitamin K (mcg)
Kale, boiled, drained	1 cup	1062
Spinach, frozen, boiled, drained	1 cup	1027
Spinach, boiled, drained	1 cup	889
Broccoli, boiled, drained	1 cup	220
Brussel sprouts, boiled, drained	1 cup	218
Cabbage, boiled, drained	1 cup	163
Spinach, raw	1 cup	145
Coleslaw, fast food	1 cup	135
Broccoli, raw, chopped	1 cup	93
Asparagus, boiled, drained	1 cup	92
Green peas, canned, drained	1 cup	63
Lettuce, green leaf, raw	1 cup	46
Vegetables, mixed, frozen, boiled, drained	1 cup	43
Blueberries, frozen, sweetened	1 cup	41
Green peas, frozen, boiled	1 cup	38
Celery, raw	1 cup	30
Marinara sauce for pasta, ready-to-serve	½ cup	18

Cucumber, with peel, raw	½ cup	9
Olive oil	1 Tbsp	8
Tuna fish, white, canned in oil, drained	85 g	6
Kiwi, raw	1 fruit	5
Pistachios, dry roasted, salt added	28 g (47 nuts)	3.7
Tea, brewed, prepared with tap water	177 mL	0

Table 1.7: The vitamin K content in different foods[10]

Drinking alcohol slows down warfarin metabolism posing a higher bleeding risk. But, drinking heavily potentially decreases the anticoagulant effect of warfarin.

Pomegranate juice is predicted to increase the INR, potentiating the effects of warfarin. Cranberry juice potentially increases the anticoagulant effect of warfarin and should be avoided. Rapid changes in diet and alcohol consumption can affect the anticoagulant effect of warfarin. (BNF, 2021)

[10] A selection of foods taken from Warfarin and Vitamin K [Internet]. Ann Arbor, MI: University of Michigan Health; 2020 [cited Aug 10]. Available from: https://www.uofmhealth.org/health-library/abo1632.

Smoking may interfere with warfarin metabolism through enzyme induction. This leads to a poor anticoagulation control. INR is lowered, giving rise to an increased thrombotic risk. Patients who have a change in their smoking habits should be monitored. (Stading *et al.,* 2007; Nathisuwan *et al.,* 2011)

Apixaban can be taken with or without food. Dabigatran and rivaroxaban should be taken with food to decrease occurence of dyspepsia and increase absorption respectively.
Since NOACs do not affect vitamin K cycle, there are no restrictions on green leafy vegetables or grapefruit juice. Alcohol use should be moderated due to the increased risk of bleeding. The literature does not specify whether smoking has a direct effect on the metabolism of NOACs. (Douketis *et al.,* 2014)

1.3.7 Summary

	Warfarin	Apixaban	Dabigatran	Rivaroxaban
Indication	Valvular- and NV-AF	NVAF only		
Frequency of administration	Once daily	Twice daily	Once or twice daily (depending on indication)	
Mode of action[11]	VKA	Direct factor Xa inhibitor	Direct thrombin inhibitor	Direct factor Xa inhibitor
Dosing[12]	Variable	Fixed		
Pro-drug	No	No	Yes	No
Bioavailability (%)[12]	100	50	6.5	80 – 100 (with food)
Protein Binding (%)[13]	99	87	35	92-95
Onset of action[11,12]	Slow	Rapid		
Duration of anticoagulant effect[12]	Long	Short		
Half-life (hour)[12]	20-60	5-6	11 up to 14 – 17	5-9 up to 11-13

[11] Mekaj *et al*, 2015

[12] Wadhera *et al*., 2014

[13] Mueck *et al*, 2013

Metabolism route	Hepatic	Hepatic[14]	Hepatic	Hepatic
Elimination route	Renal	Mainly biliary, renal	Mainly renal, faeces	Renal, faecal
DDIs[11,12,13]	Many	Few		
Food interactions[11,12,13]	Yes	No		
Routine anticoagulant monitoring	Yes (INR)	No		
Routine laboratory monitoring[12]	Baseline PT, change in patient's clinical condition	No	Renal function tests (CrCl)	No
Reversal agent[12]	Phytomenadione	Andexanet alfa	Idarucizumab	Andexanet alfa
Cost [12]	€	€€€		

Table 1.8: Characteristics of the different oral anticoagulants

All patients initiated on warfarin treatment should be well-educated about the risks and benefits of their new treatment. It is important to educate both the patient and the family members (or care givers) about symptoms of adverse effects including bruising and bleeding. This also applies to patients taking NOACs.

[14] Byon *et al.*, 2019

Patients should always remind their healthcare professional (HCP) that they are taking warfarin. Particularly, if they are to start new medications or supplements [both over the counter (OTC) and prescription only medicines (POM)]. Lifestyle changes, also warrant advising a HCP. Warfarin dose may need to be reduced or stopped before undergoing dental interventions.

Wofford *et al,* 2008 stated that "patient education is an essential component in quality management of the anticoagulated patient." In their study, Cao *et al.*, 2020, evaluated patients' level of knowledge with regards to their warfarin treatment. It was found to be moderate. It was concluded that level of knowledge significantly affects anticoagulation and INR control. Education is vital for successful treatment, particularly in patients new to warfarin. Nonetheless, education should be ongoing.

1.4 Which oral anticoagulant for which patient

Different patients present with different comorbidities, drug history and lifestyles. No drug, or in this case, anticoagulant is suitable for all patients. All patient factors should be taken into consideration. It is also important that from time to time, treatment is reviewed to analyse patient's compliance, if there are any new conditions or need to alter treatment. Choice of oral anticoagulant should be patient-centred.

Characteristic	**Drug choice**	**Rationale**
Mechanical valve or valvular AF[15]	Warfarin	NOACs not indicated yet.
Liver dysfunction with increased INR[15,16]	Warfarin	NOACs are metabolised hepatically.
Poor compliance[15]	Warfarin or nothing*	Missed doses are of greater consequence with the shorter-acting NOACs than warfarin.
Stable on warfarin[15]	Warfarin	Consider switching at patient's request only.
CrCl less than 30 mL/min[16]	Warfarin	Several studies suggested that NOACs are associated with a higher risk of bleeding in AF patients with renal insufficiency.

[15] Weitz *et al.*, 2012

[16] Pokorney *et al,* 2013

Weight < 60 kg or > 120 kg[16,17]	Warfarin	Limited efficacy and safety date on use of NOACs. Insufficient exposure of NOACs in obese subjects caused by pharmacokinetic changes.
Moderate renal insufficiency (CrCl between 30 and 49mL / min)[18,19]	Apixaban or rivaroxaban	A reduction in risk of bleeding compared to warfarin.
Dyspepsia or upper GI symptoms[15]	Rivaroxaban or apixaban	Dabigatran is associated with dyspepsia (5 – 10 % of patients)
Recent GI bleed[15,20,21]	Apixaban	The other NOACs and warfarin are associated with a higher risk of GI bleeding.
Anticoagulation in ACS[22]	Rivaroxaban, Warfarin	The other NOACs are not yet indicated in ACS.

* For some patients who are not adherent to instructions, the risk of any anticoagulant therapy may outweigh any benefits.

Table 1.9: Choice of oral anticoagulant based on patient characteristics

[17] Martin *et al.,* 2016

[18] Heidbuchel *et al.,* 2013

[19] Gui *et al.,* 2019

[20] Hammwöhner *et al.,* 2020

[21] Oh *et al.,* 2021

[22] Robinson *et al.,* 2017

1.5 Switching from warfarin to a NOAC

Based on the literature mentioned above, warfarin patients with NVAF may benefit from switching to a NOAC. This is dependent on patient factors, presence of contraindications and when NOAC treatment is financially feasible for the patient.

When switching from warfarin to apixaban or dabigatran, warfarin should be discontinued and NOAC commenced as soon as INR is below 2.0.[23,24] Switching from warfarin to rivaroxaban depends on the indication. If anticoagulation is indicated for the treatment and prevention of recurrence of DVT and PE, warfarin should be stopped and rivaroxaban initiated once INR is equal to or less than 2.5. If the indication is for stroke and systemic embolism prevention, warfarin should be stopped and rivaroxaban initiated once INR is equal to or less than 3.0.[25]

[23] Eliquis 5 mg film-coated tablets [Internet]. EMC; 2021 [cited 2021 Aug 18]. Available from: https://www.medicines.org.uk/emc/product/2878/smpc.

[24] Pradaxa 150 mg hard capsules [Internet]. EMC; 2020 [cited 2021 Aug 18]. Available from: https://www.medicines.org.uk/emc/product/4703/smpc.

[25] Xarelto 20mg film-coated tablets [Internet]. EMC; 2021 [cited 2021 Aug 18]. Available from: https://www.medicines.org.uk/emc/product/2793/smpc.

1.6 Aims and objectives

This study aims to:

- identify and compare the number of patients on warfarin and NOACs from selected pharmacies.
- assess the level of knowledge general practitioners (GPs) and pharmacists have on NOACs.
- gather feedback from warfarin patients regarding their adherence to treatment and INR monitoring, awareness on existence of NOACs and willingness to switch to a NOAC.

CHAPTER 2

METHODOLOGY

2.1 Locating and contacting the pharmacies

A number of community pharmacies were conveniently sampled, from each of the five statistical districts; Northern, Northern Harbour, South Eastern, Southern Harbour and Western. The managing pharmacist of each pharmacy was contacted and a brief overview of the study was provided. After confirmation of participation, each pharmacy was asked to provide data of how many patients they have on warfarin and NOACs. For each district where more than one pharmacy participated, the average of patients was calculated.

2.2 Formulating questionnaires

Three questionnaires were formulated and validated (Appendix I, II, III, IV). The first two questionnaires were developed to analyse the prescribing and recommending habits of NOACs by GPs and pharmacists respectively. The HCP's perception and knowledge on this new class of drugs were also evaluated. The questionnaires were validated by a panel of experts consisting of two doctors and two pharmacists. HCP questionnaires were filled in by GPs and pharmacists from different areas of Malta and Gozo.

The third questionnaire was formulated aimed for warfarin patients. The questionnaire contains two sections; section A and B. Section A analyses patient demographics, their anti-coagulant history and adherence to treatment and monitoring. Section B is about patient's awareness of alternative treatment, whether they have spoken to their GP about this treatment, and if they would be willing to switch and pay for the new treatment in the case that NOACs are suggested.

Question A6 ii was designed based on the Fagerstrom Test for Nicotine Dependence (FTND).[26] Question A7 ii (a and b) were adapted from the Alcohol Use Disorders Identification Test (AUDIT).[27] The questionnaire was validated by a panel made up of two pharmacists and one lay person who is on warfarin treatment. The questionnaire was also translated into the Maltese language.

The research ethics and data protection (REDP) form was completed and submitted to the faculty research ethics committee (FREC) of the faculty of Medicine and Surgery. FREC confirmed that the self-assessment resulted in no issues and therefore the application was for record purposes only and not for review (Appendix IV). This research is in conformity with the University of Malta's Research Code of Practice and Research Ethics Review Procedures.

Patient questionnaires were distributed to the pharmacies. Once warfarin patients presented at the pharmacy, they were asked to voluntary participate in the study and fill in the questionnaire with the help of the pharmacist on duty. The only criteria for patients to be able take part in this study was to be 18 years and older.

All collected questionnaires were given a unique code. Data was inputted in Microsoft® Excel (2013).

[26] Instrument: Fagerstrom Test For Nicotine Dependence (FTND) [Internet]. NIDA CTN Common Data Elements; 2014 [cited 2021 Aug 16]. Available from: https://cde.drugabuse.gov/instrument/d7c0b0f5-b865-e4de-e040-bb89ad43202b.

[27] AUDIT Interview Version [Internet]. NIDA CTN Common Data Elements; 2014 [cited 2021 Aug 16]. Available from: https://cde.drugabuse.gov/instrument/f355611c-0ff2-036f-e040-bb89ad435374.

CHAPTER 3

RESULTS

3.1 Warfarin vs NOACs patients

One pharmacy was selected from each of the Northern, Northern Harbour and South Eastern Districts. Two pharmacies participated from the Southern Harbour District whereas from the Western District three pharmacies were included in the study. As explained in section 2.1 above, an average was calculated for the last two mentioned districts. The results of warfarin and NOACs patients are displayed in Figure 3.1 below.

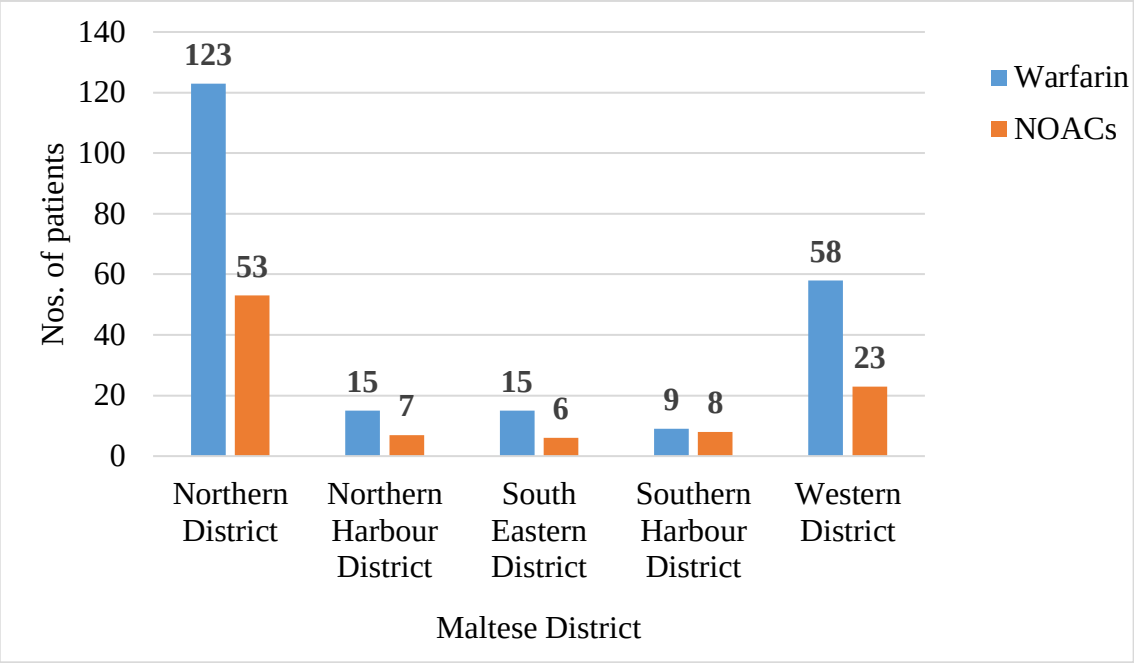

Figure 3.1: The number of patients on the different oral anticoagulants from different districts

3.2 Questionnaire for HCPs

A total of 21 GPs and 25 pharmacists completed the HCP questionnaire.

Out of the 21 GPs, only 2 said that they do not have any patients on NOACs. All 25 pharmacists have NOAC patients, however one did not indicate how many. The amount of patients on NOACs HCPs have are displayed in figure 3.2 below.

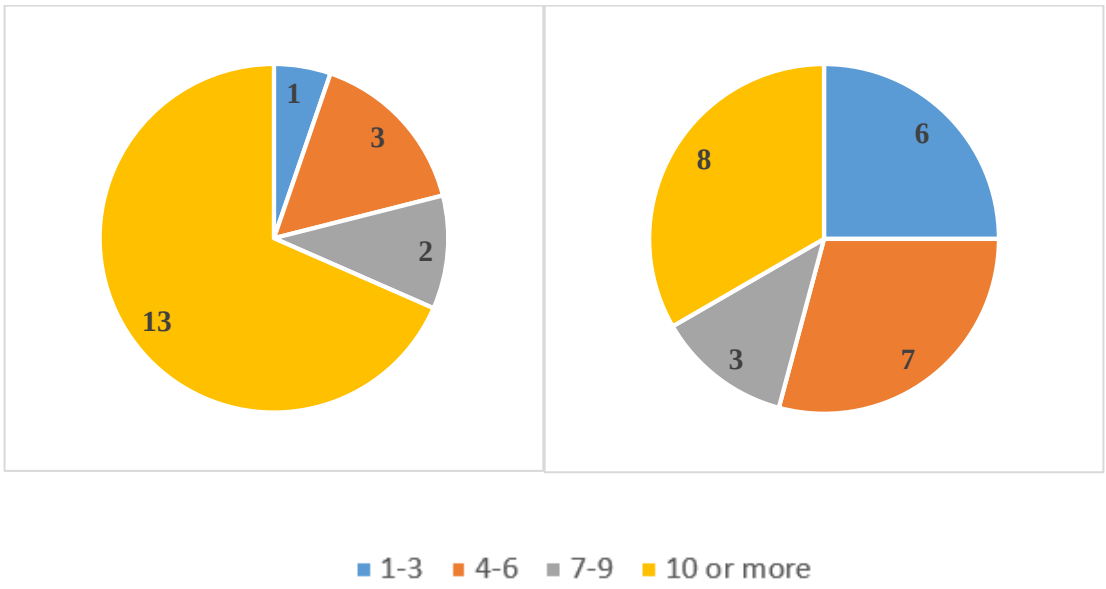

Figure 3.2: The amount of patients GPs (left) and pharmacists (right) have on NOACs

When asked whether they have ever prescribed or recommended NOACs, 16 GPs and 20 pharmacists replied yes respectively. Three GPs and 4 pharmacists replied in the negative. The remaining 2 GPs and 1 pharmacist ticked both yes and no as there were instances when they would have prescribed or recommended NOACs but due to other reasons they did not. Both yes and no answers were supported by reasons. Each HCP could tick more than one answer therefore displayed amounts represent popularity of choice.

	GPs	Pharmacists
Patients experiencing side effects and or adverse drug reactions (ADRs) with warfarin	9	6
Patients having difficulty in attending clinics for INR monitoring	16	19
Patients having difficulty in adjusting to changes in doses	7	13
Others	8	7

Table 3.1: Reasons for which GPs and pharmacists prescribe and recommend NOACs respectively

Other reasons given included informing patients of alternatives, young, active adults and patients going abroad for long time periods, patient convenience, less ADRs, less drug and food interactions. Five pharmacists replied that they did not recommend NOACs if patient is well controlled with warfarin. Two pharmacists said that they are not well informed about NOACs. The most popular reason, chosen by 4 GPs and 4 pharmacists

was that the patient did not afford buying NOACs. Other reasons were when there is a valve replacement and history of ADRs with NOACs.

HCPs were asked to mention instances when they consider prescribing and recommending NOACs. Results are displayed in Figure 3.3 below. Other reasons included when treatment is financially feasible for the patient.

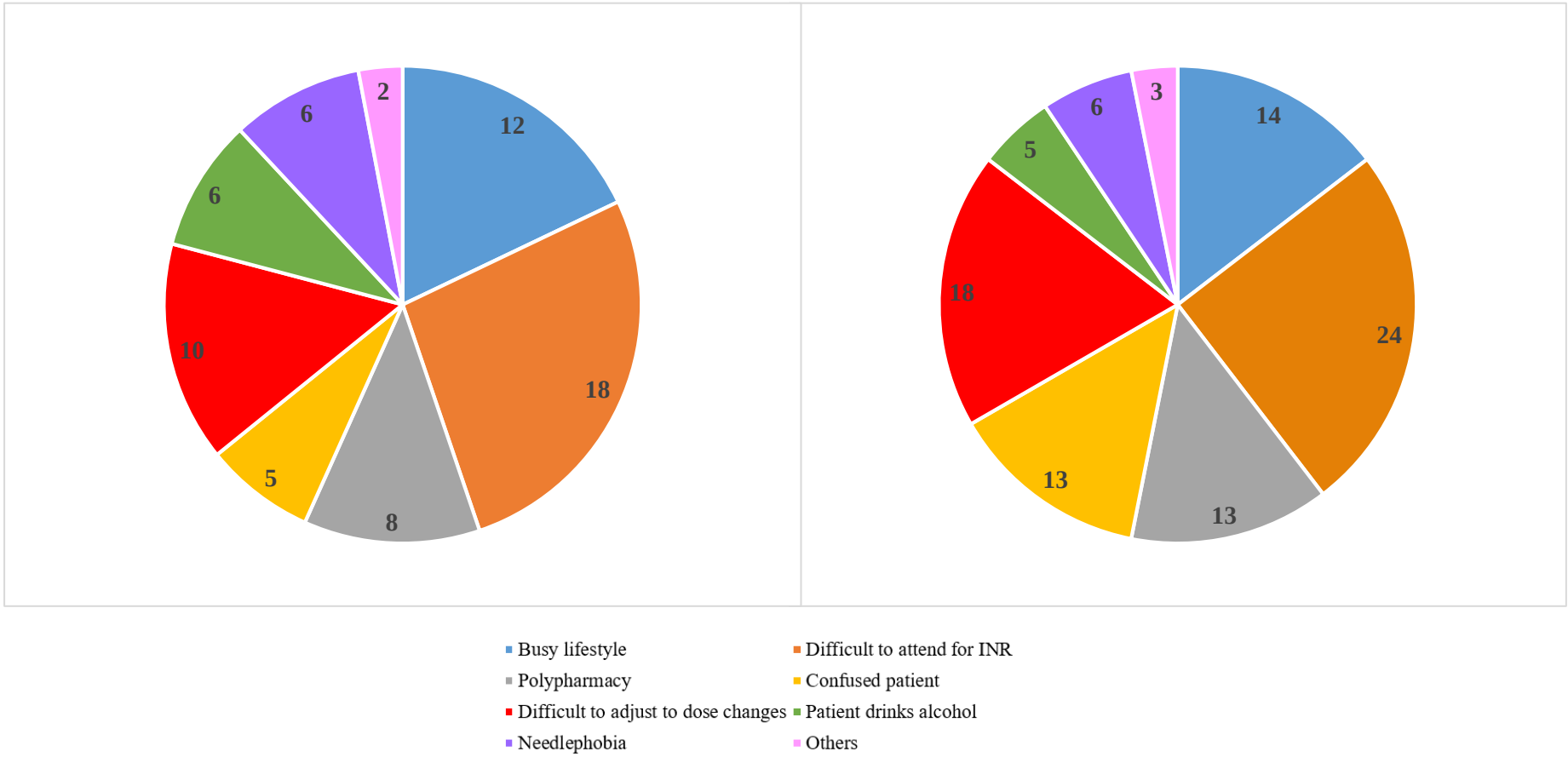

Figure 3.3: Instances when GPs (left) and pharmacists (right) consider prescribing and recommending NOACs (respectively)

When asked if they had ever had complaints from warfarin patients regarding their treatment, 19 GPs and 19 pharmacists answered yes. One pharmacist did not answer this question. Other complaints included fear of ADRs due to uncontrolled INR, mainly bruising and bleeding, and concern about polypharmacy.

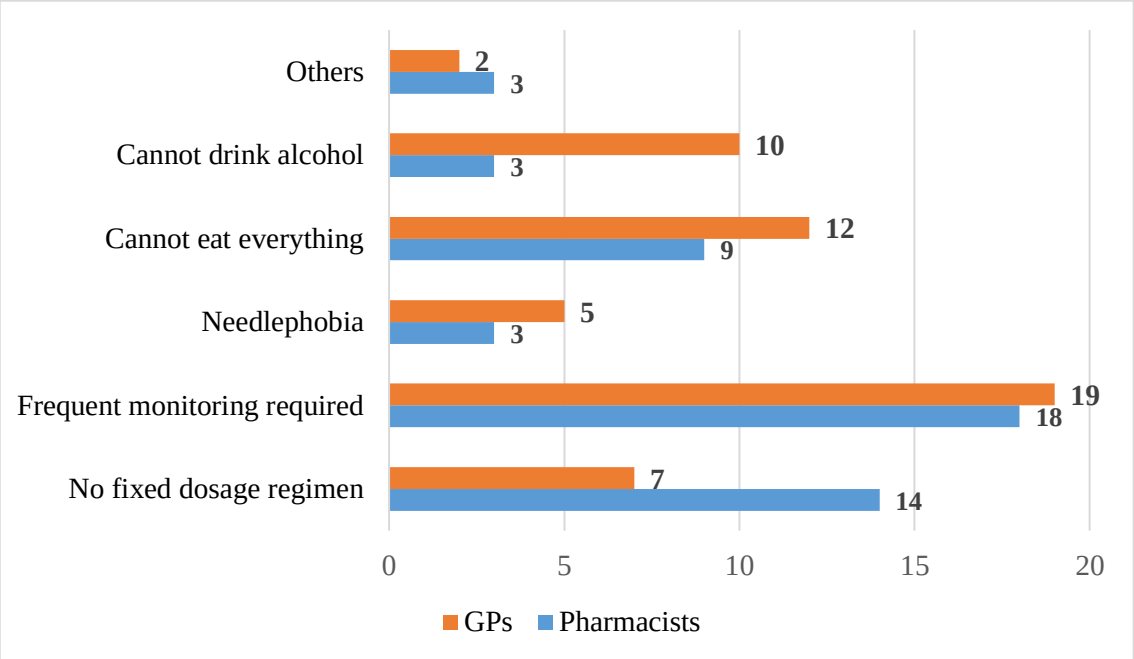

Figure 3.4: The frequency of complaints GPs and pharmacists have had from warfarin patients

Seventeen GPs and 19 pharmacists had patients enquiring about NOACs. One pharmacist did not provide an answer for this question. Out of all the 46 HCPs, one pharmacist did not know what NOACs are indicated for. Eighteen GPs and 21 pharmacists know when NOACs are more beneficial to patients when compared to warfarin. The remaining HCPs replied in the negative. All HCPs think that NOACs improve the quality of life of patients except for one pharmacist who was doubtful particularly due to their side effect profile.

With regards to the question whether in their opinion, patients are willing to pay the price of NOACs, 13 GPs and 14 pharmacists replied yes. Four GPs and 9 pharmacists replied in the negative. The remaining HCPs were unsure. Although the majority of HCPs replied yes, in their reasoning they did mention that not all patients can afford buying NOACs particularly the elderly relying on a small income. Advantages pointed out that may encourage patients switching to a NOAC were fixed dosing, safety, no need for regular monitoring, more freedom with lifestyle and that patients are willing to pay for the best treatment for them.

Twenty GPs and 19 pharmacists think that NOACs should be included in the government's outpatient's formulary list. The remaining 7 HCPs were either unsure or responded with a definite no. The reasons provided by those answering yes included that NOACs are still expensive for patients and that probably they would be cheaper for the government in the long run as they reduce strain on the healthcare system. A GP whose answer was no reasoned that locally, we have an over generous system. The pharmacists that answered no argued that introducing NOACs on the outpatients formulary would result in less income to the pharmacies, particularly those who are owners.

Eleven GPs and 12 pharmacists do not think that NOACs should be given priority over other drugs to be included in the outpatients formulary. Ten GPs and 12 pharmacists do think that they should be given priority. One pharmacist was unsure of this. Drugs that HCPs think should be prioritised over NOACs include sacubitril, dapagliflozin, drugs for mental health and autoimmune disorders, drugs for which conditions there are no other alternatives available and chemotherapeutic drugs. The latter being the most popular. Two GPs argued that cheap medicines that are easily affordable to the general public

should be removed from the outpatients formulary and instead more expensive drugs that are less affordable (such as NOACs) are introduced.

HCPs were given four statements on NOACs, each to be ticked if they think they have enough knowledge about the subject. Results are displayed in Figure 3.5 below.

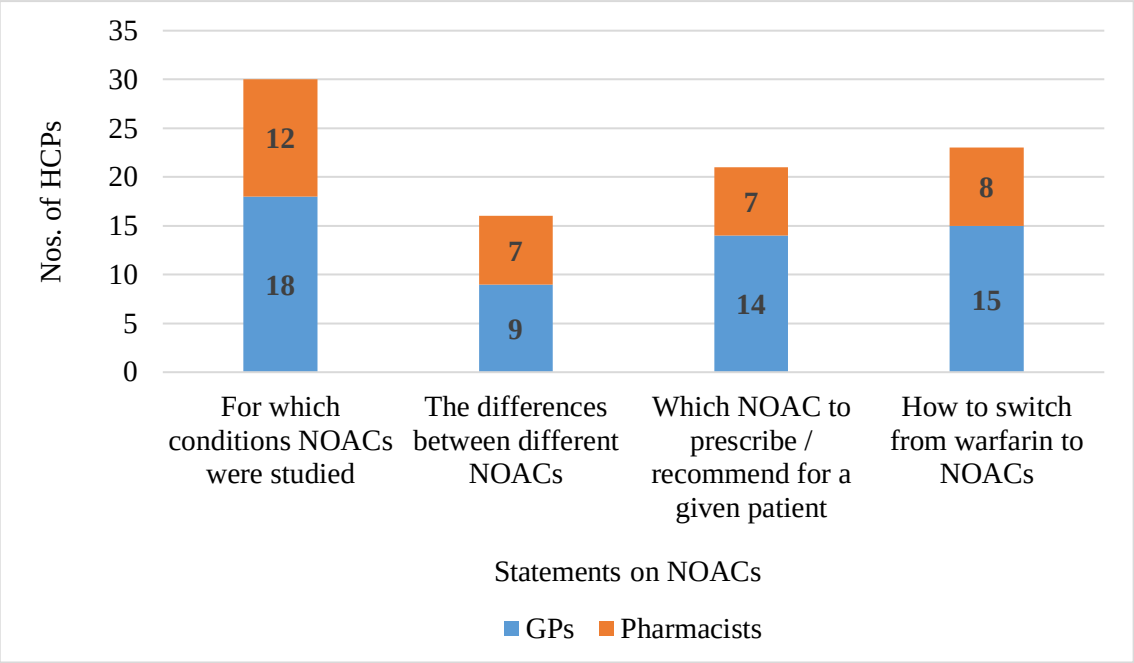

Figure 3.5: HCPs' knowledge on different aspects of NOACs

The last question was whether HCPs think more information is required from medical representatives. Seven GPs and 17 pharmacists responded in the affirmative. One pharmacist did not answer this question.

3.3 Questionnaire for warfarin patients

A total of 76 questionnaires were completed of which 47 were males and 29 were females. The ages are displayed in Figure 3.6 below. None of the patients were aged between eighteen and twenty-nine years.

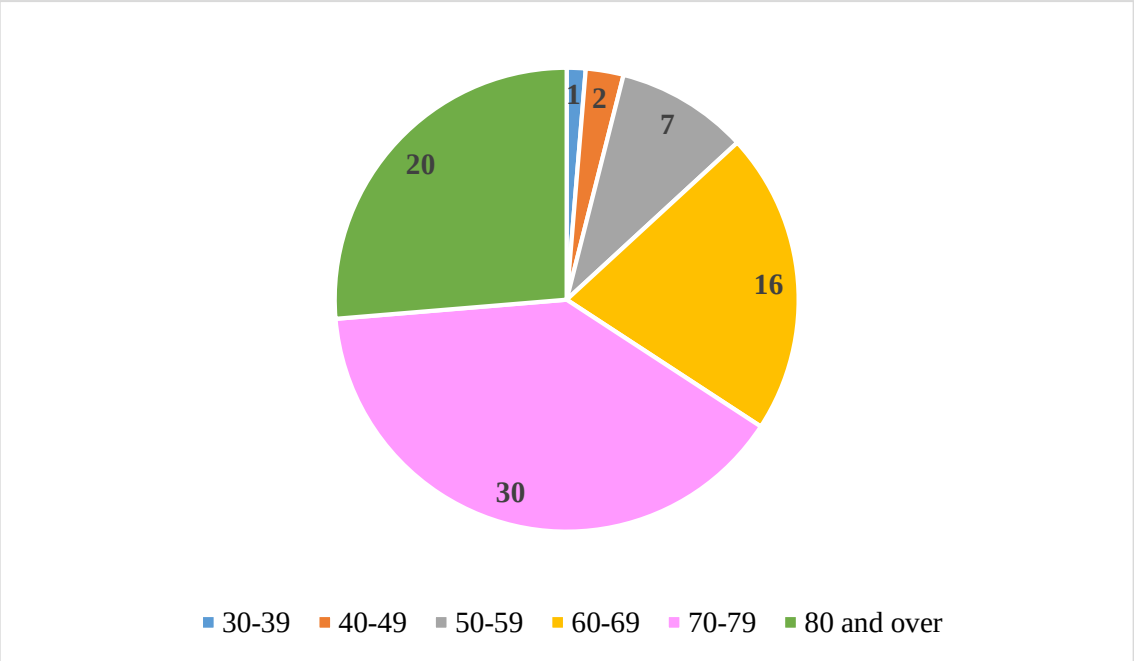

Figure 3.6: Amount of interviewed patients for each age group

Patient's current locality was recorded. Localities were then categorised by districts and tabulated in Table 3.3 below.

Maltese District	Number of Patients
Northern	12
Northern Harbour	8
South Eastern	10
Southern Harbour	26
Western	20

Table 3.2: The number of patients interviewed according to their district

Regarding patient's level of education, 27 of them attended up till primary school, 35 secondary, 8 post-secondary and 6 till tertiary. The patient's length of warfarin treatment is displayed in Figure 3.7 below. None of the interviewed patients have been using warfarin for less than 6 months.

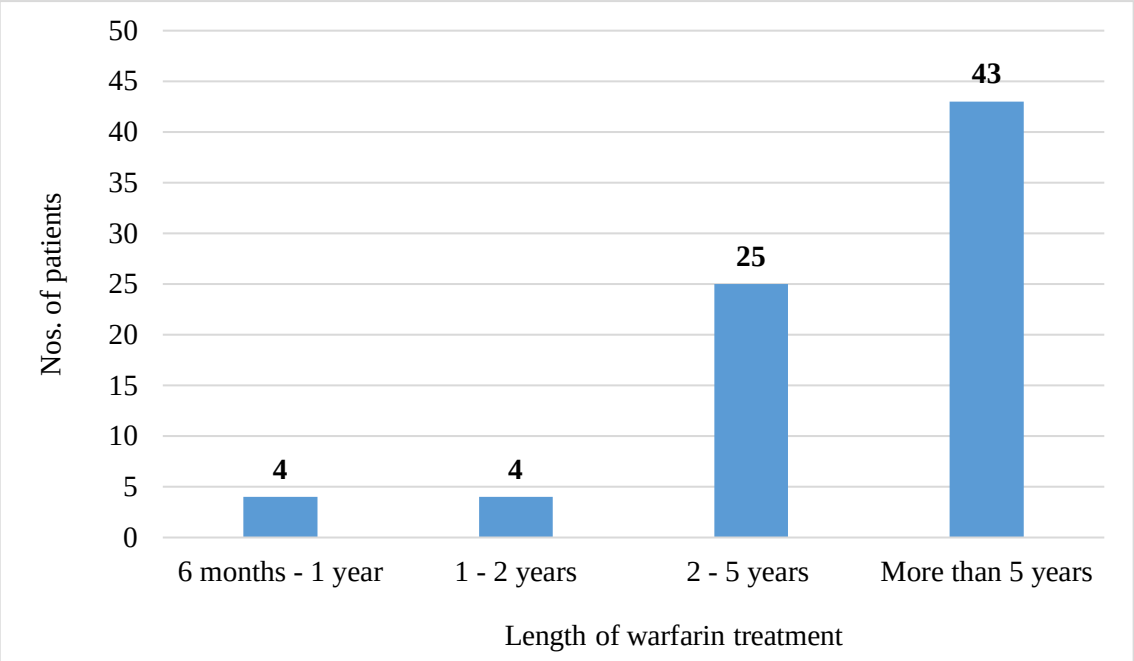

Figure 3.7: Number of warfarin patients and their length of treatment

Nine of the 76 patients are smokers. Out of these 9 patients, 3 smoke 10 cigarettes or less daily, 4 smoke 11 to 20, 1 smokes between 21 and 30 and 1 smokes 31 or more cigarettes daily. Patients were asked about their drinking habits, frequency and amount of drinks consumed in a typical day.

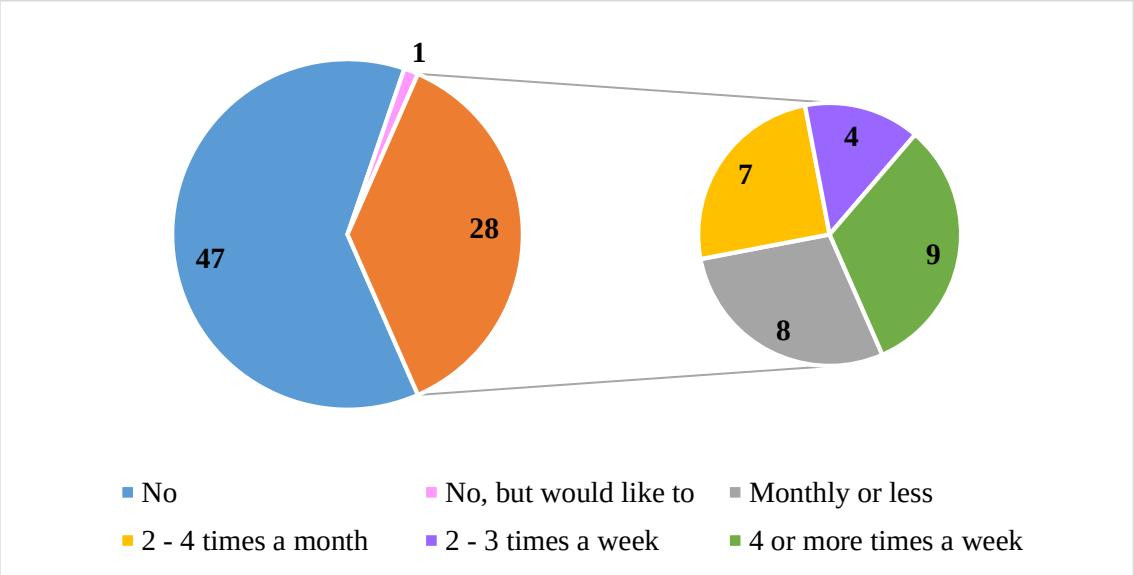

Figure 3.8: Patients and their alcohol habits and drinking frequency

Twenty-one out of the 28 patients that consume alcohol drink 1 or 2 drinks on a typical day. Six consume 3 or 4 drinks and only 1 patient drinks 5 or 6 drinks. None of the patients consume more than 6 drinks on a typical day.

When asked about green leafy vegetables and their consumption, 38 (half of the total patients interviewed) replied that they do consume vitamin K containing foods such as broccoli, cabbage and spinach. The remaining 38 do not consume any vitamin K containing foods. Five of these patients said that they would however, like to consume such foods. Figure 3.8 below represents the frequency of consumption.

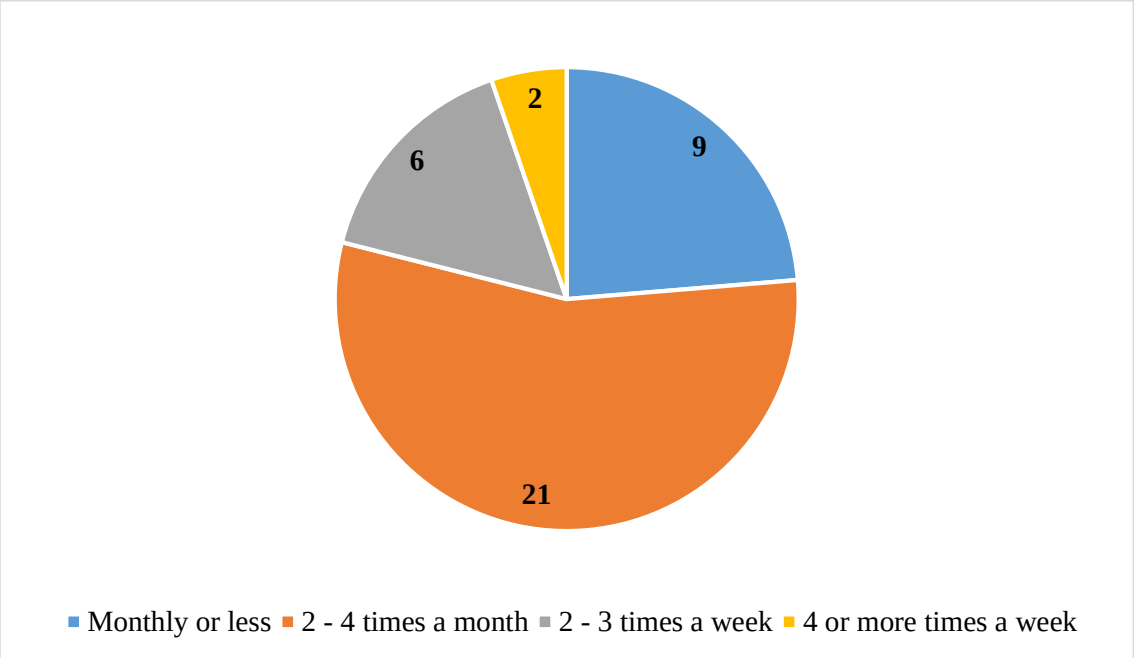

Figure 3.9: The amount of patients ant their frequency of consumption of vitamin K containing foods

Fourteen out of the 76 patients taking part in this research stated that they have needlephobia. Eleven patients do find it difficult to attend for their INR test when this is not carried out through domiciliary care. A total of 8 patients missed their INR test in the

past 6 months. Reasons were mostly linked to COVID-19 or being unable to go due to sickness. Other reasons included work and a busy lifestyle. The latter reasons were noticed in age groups younger than 60.

Twelve patients do find it difficult to adapt to change in doses. Five patients had skipped their warfarin dose once in the previous two weeks at the time of questioning. Two patients required hospitalisation in the previous 6 months, at the time of questioning. Reasons for hospitalisation were high INR and frequent epistaxis. Results from section B of the patient questionnaire are displayed in Figure 3.9 below.

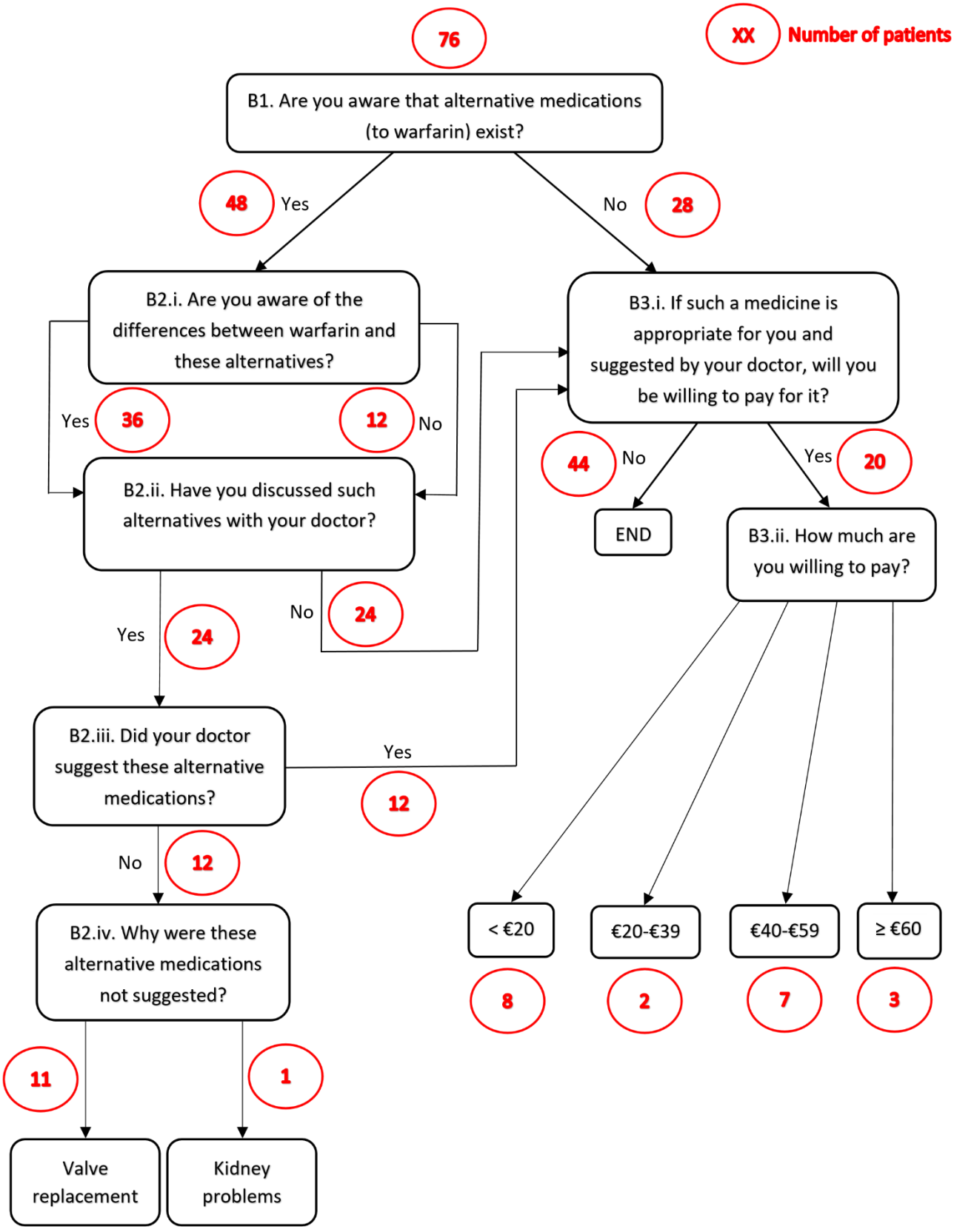

Figure 3.10: Results from Section B of the patients questionnaire

CHAPTER 4

DISCUSSION

4.1 Background

Locally, warfarin is the only oral anticoagulant that is listed on the government's outpatient's formulary list[28], entitled to patients with cardiac arrhythmias, cerebrovascular disease, chronic heart failure, chronic liver disease, ischaemic heart disease, lupus erythematosus, malignant disease and peripheral vascular disease, via the Pharmacy of Your Choice (POYC) Scheme. As a result, those patients opting to start or switch to anticoagulation with a NOAC have to commit to buy the treatment from their own money.

For those patients not entitled to warfarin or entitled but still wish to buy their warfarin treatment, the average cost of all three doses is € 2.78 for a box of twenty-eight tablets. On the other hand NOACs are much more expensive. The price ranges from €54 (cheapest generic) to €110 depending on the NOAC, dose, dosage regimen and pack size according to the indication. The most commonly used NOAC locally is rivaroxaban followed by apixaban. The recent introduction of the generics and therefore the reduction in price, has increased accessibilty to certain patients who did not afford or found the branded version expensive. This recent increase in patients changing to NOAC treatment was also highlighted by a number of pharmacists participating in the study. Pharmacists stated that patients were willing to change to the generic product.

[28] Outpatients Formulary List [Internet]. Health.gov.mt; 2021; [cited 2021 Aug 14]. Available from: https://deputyprimeminister.gov.mt/en/pharmaceutical/Documents/GFL/outpatients_gfl_may_2021.pdf.

As seen in Figure 3.6, the majority of interviewed patients were 70 years and over. This means that the only income for these patients is their monthly pension, which has to support their daily living expenses as well as the buying of other medicines. For these reasons, even though NOACs may be appropriate and more convenient for these patients, they still opt to use warfarin as they are entitled to free treatment and monitoring. This is further supported by Figure 3.1 where all five districts have more patients on warfarin than on NOACs.

4.2 Outcome from HCPs and patients questionnaires

Most HCPs indicated that the popularity of NOACs have increased in the past years particularly due to the COVID-19 pandemic. This is backed up by the number of patients most of the HCPs claimed to have on NOACs (figure 3.2). Warfarin patients, particularly the vulnerable seemed to be more reluctant to go for their INR monitoring during the pandemic so whenever possible they resorted to NOACs as an alternative treatment to warfarin.

The reasons why GPs and pharmacists prescribe and recommend NOACs respectively (table 3.1) are the main advantages of NOACs over warfarin. The reasons why the HCPs did not prescribe or recommend are mainly the disadvantages posed by NOACs, the main one being their high cost. More than half of the patients interviewed would not pay for NOAC treatment (figure 3.10), if this treatment is suitable for them. This was more common in those patients who have been on warfarin treatment for more than 5 years. This showed that they feel peace of mind with monitoring and that they would be worried and feel unsafe with NOACs. The remaining amount would not switch due to financial

reasons. Patients stated that they would switch to NOACs if they are introduced on the outpatients formulary (and suitable for them).

Although, the most common complaint HCPs have received from warfarin patients (figure 3.4) was the need for frequent INR monitoring, the research has shown that only a few of the interviewed patients complain about this. Having the majority of patients elderly, who are retired, it is not so difficult for them to attend for their INR test. However, it is good to note that INR testing is also being provided through domiciliary care; both bloodletting and POCT. This eliminates inconvenience of having to go to the Anticoagulation Clinic (ACC) within Mater Dei Hospital (MDH). For those who do not have domiciliary care, they have the convenience to attend for their test at the nearest government district dispensary. These two initiatives have led to the high patient's adherence to monitoring. For those still attending MDH for their test, it may be an inconvenience to the patient's family if they rely on them for transport.

The HCP questionnaire has shown that the majority of HCPs interviewed agree that NOACs should be included in the outpatients formulary. Although NOACs are much more expensive than warfarin to procure, introducing them in the outpatients formulary would be an initiative to patients to switch (whenever possible). This in turn would reduce the costs of consumable equipment and labor required to perform INR tests. Other costs that would be bypassed include time and personnel needed to communicate results and change in doses (if needed). Switching from warfarin to NOACs means less DDIs and possibly less ADRs and therefore less need for hospitalisation, which is also an indirect cost of warfarin.

Education on NOACs is still lacking amongst HCPs, with pharmacists being less knowledgeable in general (figure 3.5). Thirty out of the 46 HCPs stated that they have enough knowledge on the conditions for which NOACs were studied. This was the most knowledgable out of the four mentioned statements. The least known was the existing differences between the different NOACs, with only 16 HCPs being knowledgable about this. Medicine is ever-changing undergoing continual development. HCPs should keep themselves updated on a regular basis and be able to provide accurate information to their patients.

More than half of the interviewed patients are aware of the availability of NOACs (figure 3.9). Figure 4.1 below shows the correlation (if any) between the level of education and awareness on NOACs.

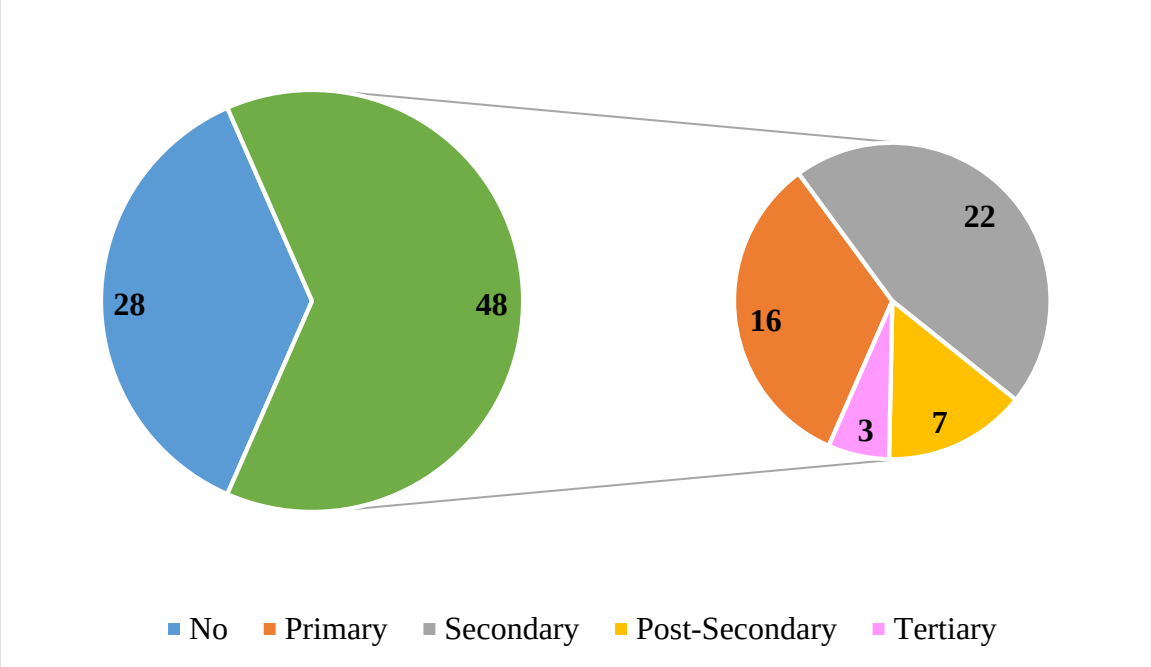

Figure 4.1: Patients awareness of NOACs and their level of education

There seems to be no correlation between the level of education and awareness on NOACs. The higher number of patients that know about NOACs, shows that in general, patients are getting more informed. The results have shown that the high majority of these patients have spoken to their GP (figure 3.10). This shows that patients are getting more involved in the decision-making when it comes to the choice of their treatment.

Although all patients are aware of the possible risks of consuming vitamin K containg foods, half of them still opt to consume such foods. Alcohol consumption (figure 3.8) and cigarette smoking are still a habit amongst a number of warfarin patients. It could be the case that this lifestyle leads to the need of more frequent INR testing due to fluctuations, but this study did not take this factor into account. This study identified 2 patients that were admitted to hospital. These 2 patients are non-smokers and do not drink any alcohol and one of them consumes vitamin K containing foods. These 2 patients were admitted to hospital due to inadequate dosing and epistaxis. Other patients have experienced bruising but did not require hospitalisation.

Patients do not seem to be bothered by the use of needles for routine INR monitoring. Patients did mention that since it is done routinely, there is nothing they can do about it and that they had to get used to it. It was noted that a good portion of the interviewed population do not get tested traditionally but using a POCT such as CoaguChek®, where a fingerstick is used. Being less invasive, it is more acceptable to patients and results are conveyed at the time of testing. In this way, compared to the traditional system, costs are already reduced as discussed by Zammit *et al.*, 2011.

Although most patients do not find it difficult to adapt to dose changes, patients do use aids to help them in their daily dosing. Such aids include pill boxes and jotting doses on calendar. In the previous two weeks at the time of questioning, 5 patients missed their dose completely. Pill boxes help patients remember about their dose and some also set reminders on their electronic devices. Although not completely missed, there were instances when patients had temporarily forgotten their medicine and as a result ended up taking it later than usual.

4.3 Increasing awareness and education

A principal goal of this study was to increase awareness and education on the different oral anticoagulants available amongst patients. This goal was primarily met by the patient's participation in the study; both by filling out the questionnaire and communicating with the pharmacist with regards to their anticoagulant treatment. All patients gave positive feedback.

A brief overview of this research was aired on the national TV programme "It-Teżi". The available oral anticoagulants and the differences between the two classes were explained. This was laid out in simple layman's terms for the understanding of the general public, particularly the geriatric patients. This helped reaching more patients and caregivers who were not targeted by the questionnaire.

4.4 Limitations of the study

Observed limitations of the study include the following:

- The amount of pharmacies participating in the study was not equal for each district. Averages of the number of patients on warfarin and NOACs would be more accurate. Similarly, the amount of patients interviewed were not the same for each district. Any correlations to the districts would have been more evident (if any).

- A limitation that is not easily overcome regards the HCPs interviewed. Stated amounts of patients may be common to more than one GP or pharmacist. HCPs were not asked about their level of education (eg. Diploma, Masters, Doctorate level for pharmacists) or for how long they have been practicing. This may relate to the fact to how updated a HCP is with ongoing new studies.

- Warfarin patients were not asked how controlled they are (eg. every how many weeks they attend for their INR test). This could have showed trends to lifestyle changes. For example, does a patient who smokes, drinks alcohol and / or consumes vitamin K containing foods have to test more frequently than another patient who does not? An additional question to those patients who have missed a test could have been the amount of tests that were missed.

- In this research, 12 patients were identified as ‘non-ideal’ patients for NOAC treatment. However, this number was out of the forty-eight patients who answered that they are aware of NOACs, and not out of the whole population interviewed.

NVAF may be included as an inclusion criterion. Alternatively, patients could be asked the reason for which they have started warfarin.

4.5 Way forward

Other healthcare systems particularly of European Union (EU) countries can be reviewed. This helps in understanding and comparing what is being done in other member states to help make NOACs more accessible to their patients.

An economic study would give a definite, clearer picture whether it would be viable to procure NOACs and include them in the outpatients formulary. It is important to keep in mind the portion of patients for whom NOACs are not yet indicated.

4.6 Conclusion

In conclusion, from this study, it is evident that even though warfarin has its burdens, patients are compliant to their treatment.

In the light of the introduction of generic medicines, NOACs are becoming more affordable to less financially able patients. It also gives hope that they are being considered for inclusion in the government's outpatient's formulary list and become even more accessible to all patients suitable to make the switch from warfarin to NOACs. Warfarin use will not stop here. Studies on NOACs are still ongoing and to date, NOACs are not an absolute replacement to warfarin.

Lastly, patient education and support are of utmost importance for succesful anticoagulant treatment and to safeguard our patients.

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LIST OF PUBLICATIONS AND ABSTRACTS

The below abstract was submitted for appraisal for the Maltese Cardiac Society Conference on 23rd September 2021.

Background

The Novel Oral Anticoagulants (NOACs) provide advantages over warfarin due to a predictable anticoagulant effect and lower risk of drug interactions. NOACs are higher in cost compared to warfarin and at the time of the study were not available on the Government Formulary.

Purpose

To assess the level of knowledge of health care professionals on NOACs and to assess perception of patients on warfarin regarding adherence to treatment, awareness of NOACs and willingness to switch to a NOAC.

Methods

The study was set in eight community pharmacies, conveniently sampled from each of the five statistical districts in Malta. Three questionnaires were formulated and validated; one for general practitioners (GPs), one for pharmacists and the other for warfarin patients.

Results

A total of 21 GPs, 25 pharmacists and 76 patients participated in the study. Only two GPs stated that they do not have patients on NOACs. GPs and pharmacists particularly prescribe or recommend NOACs to patients who have difficulty in attending INR clinics (16 GPs, 19 pharmacists), and those patients who are challenged due to the adjustment in

warfarin dosing required (7 GPs, 13 pharmacists). Healthcare professionals felt that they required more information on studies supporting use of NOACs in different conditions (3 GPs, 13 pharmacists) and on advice to switch patients from warfarin to NOACs (6 GPs, 17 pharmacists).

Warfarin patients stated that they find it difficult to attend for their INR test (11), missed INR test appointments in the last 6 months (8), found it hard to adapt to the changes in dosing (12). Two patients reported that they required hospitalisation in the previous 6 months due to high INR and frequent epistaxis. With regards to patient awareness of NOACs, 48 patients were aware of the alternative, with 36 being conscious of the differences compared to warfarin. Out of 64 of the total patient population, 20 were willing to pay monthly for the alternative treatment: 8 patients less than 20 Euro, 2 patients 20-39 Euro, 7 patients 40-59 Euro and 3 patients more than 60 Euro.

Conclusion

Access to NOACs is limited since their price is considered a burden by patients who are entitled to free warfarin and INR testing via the national health service. Healthcare professionals are in a position to prioritise patients who would benefit from the advantages of NOACs.

APPENDICES

Appendix I: Questionnaire for GPs

Use of Warfarin and Novel Oral Anticoagulants (NOACs)

1. A. Do you have any patients on NOACs treatment?

   Yes ☐ (Advance to question 1B)

   No ☐ (Advance to question 2A)

   B. If yes, how many?

   1 – 3 ☐

   4 – 6 ☐

   7 – 9 ☐

   ≥ 10 ☐

2. A. Have you ever prescribed NOACs?

   Yes ☐ (Advance to question 2B)

   No ☐ (Advance to question 2C)

   B. If yes, choose any reason/s from the below.

   Patients experiencing side effects and/or adverse drug reactions with warfarin. ☐

   Patients having difficulty in attending clinics for INR monitoring. ☐

   Patients having difficulty in adjusting to changes in doses. ☐

   Others _____

   C. If no, choose any reason/s from the below.

   Patients are well controlled with warfarin. ☐

   Patients do not afford buying NOACs. ☐

   Not well informed about NOACs. ☐

   Others _____

3. When do you consider prescribing NOACs?

   When patient has a busy lifestyle. ☐

   When patient finds it difficult to attend for INR monitoring. ☐

   When patient has polypharmacy. ☐

   When patient has drug-drug interactions. ☐

   When patient is confused. ☐

   When patient finds it difficult to adjust to dose changes. ☐

   When patient drinks alcohol. ☐

   When patient suffers from needlephobia. ☐

   Others _____

4. A. Have you ever had complaints from patients with respect to warfarin treatment?

   Yes ☐ (Advance to question 4B)

   No ☐ (Advance to question 5)

   B. If yes, choose any from the below.

   No fixed dosage regimen. ☐

   Frequent monitoring required. ☐

   Needlephobia. ☐

   Cannot eat everything. ☐

   Cannot drink alcohol. ☐

   Others _____

5. Have you ever had a patient that enquired information about NOACs?

   Yes ☐

   No ☐

6. Do you know what NOACs are indicated for?

   Yes ☐

   No ☐

7. Do you know when NOACs are more beneficial to the patient when compared to warfarin?

   Yes ☐

   No ☐

8. In your opinion, do you think that NOACs improve the patients' quality of life?

   Yes ☐

   No ☐

9. A. Do you think that patients are willing to pay the price of NOACs?

   Yes ☐

   No ☐

   B. Give a reason for your answer.

   _____

10. A. Do you think NOACs should be on the Government's Outpatients Formulary List?

    Yes ☐

    No ☐

    B. Give a reason for your answer.

    _____

11. A. Do you think NOACs should be given priority over other drugs to be supplied on

    the Government's Outpatients Formulary List?

    Yes ☐ (Advance to question 12)

    No ☐ (Advance to question 11B)

    B. Which drugs would you prioritise over NOACs?

    _____

12. Do you think you have enough knowledge regarding the following? (Tick where applicable.)

    For which conditions NOACs were studied. ☐

    The differences between different NOACs. ☐

    Which NOAC to prescribe for a given patient. ☐

    How to switch from warfarin to NOACs. ☐

13. Do you think that more information is required from medical representatives?

    Yes ☐

    No ☐

Appendix II: Questionnaire for pharmacists

Use of Warfarin and Novel Oral Anticoagulants (NOACs)

1. A. Do you have any patients on NOACs treatment?

   Yes ☐ (Advance to question 1B)

   No ☐ (Advance to question 2A)

   B. If yes, how many?

   1 – 3 ☐

   4 – 6 ☐

   7 – 9 ☐

   ≥ 10 ☐

2. A. Have you ever recommended NOACs?

   Yes ☐ (Advance to question 2B)

   No ☐ (Advance to question 2C)

   B. If yes, choose any reason/s from the below.

   Patients experiencing side effects and/or adverse drug reactions with warfarin. ☐

   Patients having difficulty in attending clinics for INR monitoring. ☐

   Patients having difficulty in adjusting to changes in doses. ☐

   Others _____

   C. If no, choose any reason/s from the below.

   Patients are well controlled with warfarin. ☐

   Patients do not afford buying NOACs. ☐

   Not well informed about NOACs. ☐

Others _____

3. When do you consider recommending NOACs?

   When patient has a busy lifestyle. ☐

   When patient finds it difficult to attend for INR monitoring. ☐

   When patient has polypharmacy. ☐

   When patient has drug-drug interactions. ☐

   When patient is confused. ☐

   When patient finds it difficult to adjust to dose changes. ☐

   When patient drinks alcohol. ☐

   When patient suffers from needlephobia. ☐

   Others _____

4. A. Have you ever had complaints from patients with respect to warfarin treatment?

   Yes ☐ (Advance to question 4B)

   No ☐ (Advance to question 5)

   B. If yes, choose any from the below.

   No fixed dosage regimen. ☐

   Frequent monitoring required. ☐

   Needlephobia. ☐

   Cannot eat everything. ☐

   Cannot drink alcohol. ☐

   Others _____

5. Have you ever had a patient that enquired information about NOACs?

   Yes ☐

No ☐

6. Do you know what NOACs are indicated for?

   Yes ☐

   No ☐

7. Do you know when NOACs are more beneficial to the patient when compared to warfarin?

   Yes ☐

   No ☐

8. In your opinion, do you think that NOACs improve the patients' quality of life?

   Yes ☐

   No ☐

9. A. Do you think that patients are willing to pay the price of NOACs?

   Yes ☐

   No ☐

   B. Give a reason for your answer.

   _____

10. A. Do you think NOACs should be on the Government's Outpatients Formulary List?

    Yes ☐

    No ☐

    B. Give a reason for your answer.

    _____

11. A. Do you think NOACs should be given priority over other drugs to be supplied on

    the Government's Outpatients Formulary List?

    Yes ☐ (Advance to question 12)

    No ☐ (Advance to question 11B)

    B. Which drugs would you prioritise over NOACs?

    _____

12. Do you think you have enough knowledge regarding the following? (Tick where applicable.)

    For which conditions NOACs were studied. ☐

    The differences between different NOACs. ☐

    Which NOAC to recommend for a given patient. ☐

    How to switch from warfarin to NOACs. ☐

13. Do you think that more information is required from medical representatives?

    Yes ☐

    No ☐

Appendix III: Questionnaire for warfarin patients (English)

Use of Warfarin and Novel Oral Anticoagulants (NOACs)

A. Patient demographics, Anti-coagulant History and Adherence to Treatment and Monitoring

A1. Gender

Female ☐ Male ☐ Other ☐

A2. Age (years)

18 – 29 ☐ 30 – 39 ☐ 40 – 49 ☐ 50 – 59 ☐

60 – 69 ☐ 70 – 79 ☐ 80 and over ☐

A3. Locality

_____

A4. Level of education

Primary ☐ Secondary ☐

Post-Secondary ☐ Tertiary ☐

A5. For how long have you been taking warfarin?

Less than 6 months ☐ 6 months – 1 year ☐ 1 – 2 years ☐

2 – 5 years ☐ More than 5 years ☐

A6. i. Do you smoke?

Yes ☐ No ☐

ii. If yes, how many cigarettes do you smoke per day?

10 or less ☐ 11 – 20 ☐

21 – 30 ☐ 31 or more ☐

A7. i. Do you drink alcohol?

Yes ☐ No ☐ No, but would like to ☐

ii. a. If yes, how frequent?

Monthly or less ☐ 2 – 4 times a month ☐

2 – 3 times a week ☐ 4 or more times a week ☐

ii. b. On a typical day, how many drinks do you have?

1 or 2 ☐ 3 or 4 ☐ 5 or 6 ☐

7 – 9 ☐ 10 or more ☐

A8. i. Vegetables (particularly green leafy ones) eg. broccoli, cabbage and spinach are examples of foods high in Vitamin K. Do you consume any of these?

Yes ☐ No ☐ No, but would like to ☐

ii. If yes, how often?

Monthly or less ☐ 2 – 4 times a month ☐

2 – 3 times a week ☐ 4 or more times a week ☐

A9. Do you have a fear of needles (needle phobia)?

Yes ☐ No ☐

A10. i. Do you find it difficult to attend to your INR (warfarin) test?

Yes ☐ No ☐

ii. In the past six months, did you miss going for your INR (warfarin) monitoring?

Yes ☐ No ☐

iii. If yes, why?

_____

A11. Do you find it difficult to adapt to change in doses?

Yes ☐ No ☐

A12. i. In the past two weeks, were there days when you skipped your warfarin dose?

Yes ☐ No ☐

ii. If yes, how many doses did you skip?

1 ☐ 2 ☐

3 ☐ more than 3 ☐

A13. In the last 6 months, did you require hospitalization due to warfarin treatment eg. high INR and bleeding episodes? (Eg. blood in stools, nose bleeds or unexplained bruising)

Yes ☐ No ☐

B. Awareness of Alternative Treatment

B1. Are you aware that alternative medications (to warfarin) exist?

Yes ☐ (Go to B2) No ☐ (Go to explanation and B3)

B2. i. Are you aware of the differences between warfarin and these alternatives?

Yes ☐ No ☐

ii. Have you discussed such alternatives with your doctor?

Yes ☐ No ☐ (Go to B3)

iii. Did your doctor suggest these alternative medications?

Yes ☐ (Go to B3) No ☐

iv. Why were these alternative medications not suggested by your doctor?

_____ ***(The questionnaire ends here)***

Explain the following to patients who have responded 'No' in B1 above.

The alternative medications to warfarin are known as NOACs or DOACs. The main difference is the mode of action. With the alternative medications, there is no need for INR (warfarin) monitoring and the daily dose is fixed. Not all patients taking warfarin are suggested to switch to a NOAC / DOAC. These alternative medications are currently not available for chronic use on the Government's Outpatients Formulary List.

B3. i. If such a medicine is appropriate for you and suggested by your doctor, will you be willing to pay for it?

Yes ☐ No ☐

ii. If yes, how much are you willing to pay?

Less than € 20 ☐ € 20 - € 39 ☐

€ 40 - € 59 ☐ € 60 and more ☐

Other notes :

_____

_____

_____

_____

Appendix IV: Questionnaire for warfarin patients (Maltese)

Kwestjonarju

A. Demografija tal-pazjent, Storja tal-antikoagulazzjoni u Aderenza mat-Trattament u Moniteraġġ

A1. Sess

Mara ☐ Raġel ☐ Oħrajn ☐

A2. Eta' (snin)

18 – 29 ☐ 30 – 39 ☐ 40 – 49 ☐ 50 – 59 ☐

60 – 69 ☐ 70 – 79 ☐ 80 'il fuq ☐

A3. Lokalita'

_____

A4. Livell ta' edukazzjoni

Primarju ☐ Sekondarju ☐

Post-Sekondarju ☐ Terzjarju ☐

A5. Kemm ilek tieħu l-warfarina?

Inqas minn 6 xhur ☐ 6 xhur – sena ☐ sena – sentejn ☐

Sentejn – 5 snin ☐ Iktar minn 5 snin ☐

A6. i. Inti tpejjep?

Iva ☐ Le ☐

ii. Jekk iva, kemm –il sigarett tpejjep kuljum?

10 jew inqas ☐ 11 – 20 ☐

21 – 30 ☐ 31 jew iktar ☐

A7. i. Inti tixrob alkoħol?

Iva ☐ Le ☐ Le, imma nixtieq ☐

ii. a. Jekk iva, kemm-il darba?

Darba fix-xahar jew inqas ☐ 2 – 4 darbiet fix-xahar ☐

2 – 3 darbiet fil-ġimgħa ☐ 4 darbiet jew iktar fil-ġimgħa ☐

ii. b. F'ġurnata tipika, kemm-il tazza tixrob?

1 jew 2 ☐ 3 jew 4 ☐ 5 jew 6 ☐

bejn 7 u 9 ☐ 10 jew iktar ☐

A8. i. Ħaxix (partikolarment dak li hu aħdar skur) bħal brokkoli, kaboċċi u spinaċi huma tipi ta' ikel sinjuri fil-vitmina K. Inti tikkonsma minn dan it-tip ta' ħaxix?

Iva ☐ Le ☐ Le, imma nixtieq ☐

ii. Jekk iva, kemm-il darba?

Darba fix-xahar jew inqas ☐ 2 – 4 darbiet fix-xahar ☐

2 – 3 darbiet fil-ġimgħa ☐ 4 darbiet jew iktar fil-ġimgħa ☐

A9. Inti tibża' mil-labar?

Iva ☐ Le ☐

A10. i. Inti ssibha diffiċli biex tattendi għat-test tal- INR (warfarina)?

Iva ☐ Le ☐

ii. Fl-aħħar sitt xhur, ġieli qbiżt l-appuntament tal-moniteraġġ tal-INR (warfarina)?

Iva ☐ Le ☐

ii. Jekk iva, x'kienet ir-raġuni?

_____

A11. Issibha diffiċli biex tadatta għat-tibdil fid-doża?

Iva ☐ Le ☐

A12. i. Fl-aħħar ġimagħtejn, kien hemm ġranet meta qbiżt id-doża tal-warfarina?

Iva ☐ Le ☐

ii. Jekk iva, kemm-il doża qbiżt?

1 ☐ 2 ☐

3 ☐ 3 jew iktar ☐

A13. Fl-aħħar sitt xhur, kellek bżonn tiddaħħal l-isptar minħabba t-trattament tal-warfarina eż. INR għoli jew emorraġija (bħal demm fl-ippurgar, infraġt jew tbenġil mingħajr spjegazzjoni)

Iva ☐ Le ☐

A. Għarfien ta’ Trattamenti Alternattivi

B1. Inti mgħarraf bl-eżistenza ta’ mediċini alternattivi (għall-warfarina)?

Iva ☐ (Mur B2) Le ☐ (Mur għall-ispjegazzjoni u B3)

B2. i. Inti mgħarraf bid-differenzi li hemm bejn il-warfarina u dawn il-mediċini alternattivi?

Iva ☐ Le ☐

ii. Inti ddiskutejt dawn l-alternattivi mat-tabib tiegħek?

Iva ☐ Le ☐ (Mur B3)

iii. It-tabib tiegħek issuġġerilek dawn il-mediċini alternattivi?

Iva ☐ (Mur B3) Le ☐

iv. X’inhi r-raġuni għalfejn dawn il-mediċini alternattivi ma ġewx issuġġeriti mit-tabib tiegħek?

_____*(Il-kwestjonarju jintemm hawn)*

Spjega dan t’hawn isfel lill-pazjenti li rrispondew ‘Le’ fil-mistoqsija B1 hawn fuq.

Il-mediċini alternattivi għall-warfarina huma magħrufa bħala NOACs jew DOACs. Id-differenza prinċipali hija fil-mod ta’ kif jaħdmu. Bil-mediċini l-ġodda m’hemmx għalfejn ikun hemm moniteraġġ tal-INR (warfarina) u d-doża hija waħda stabbli dejjem. Mhux il-pazjenti kollha li jieħdu l-warfarina huma ssuġġeriti li jeqilbu għal dawn il-mediċini alternattivi u nnovattivi. Preżentament, dawn il-mediċini alternattivi m’humhiex offruti għal mard kroniku b’xejn permezz tal-formularju tal-Gvern (pazjenti li ma jkunux fl-isptar).

B3. i. Jekk mediċina ta' dan it-tip tkun addattata għalik u ssuġġeritha mit-tabib tiegħek, inti lest li tħallas għal din il-mediċina alternattiva?

Iva ☐ Le ☐

ii. Jekk iva, kemm lest li tħallas?

Inqas minn € 20 ☐ € 20 - € 39 ☐

€ 40 - € 59 ☐ € 60 u iktar ☐

Noti oħra :

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_____

_____

_____

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Appendix V: Official correspondence from FREC

L-Università ta' Malta

Grazielle Camilleri <grazielle.camilleri.13@um.edu.mt>

FRECMDS_2021_163 - ID:- 9374_20072021_Grazielle Camilleri

FACULTY RESEARCH ETHICS COMMITTEE <research-ethics.ms@um.edu.mt>21 July 2021 at 12:43
To: Grazielle Camilleri <grazielle.camilleri.13@um.edu.mt>
Cc: Anthony Serracino Inglott <anthony.serracino-inglott@um.edu.mt>

Dear Ms Camilleri,

Since your self-assessment resulted in no issues being identified, FREC will file your application for record and audit purposes but will not review it.

Any ethical and legal issues including data protection issues are your responsibility.

Kindly **confirm** that you sent all the documents which you attached to the UREC form together with other documents related to your study.

Kindly note that these documents are also requested for audit purposes.

Regards,
Annalise