The Impact of a Direct Oral Anticoagulant in Cardiovascular Disease

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To my fiancée Shakeera, my mum Emily and dad George for their continued support and endless love. I owe all that I have to you mum and dad. Thank you for being the best parents in the world. Thank you Shakeera, for being my rock. Words cannot describe how lucky I am to have you in my life.

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Abstract

Novel oral anticoagulants (NOACs) have uncomplicated dosing with no need for INR monitoring and fewer possible drug and food interactions compared to warfarin, which may result in improved adherence to treatment and may offset the high retail cost of NOACs. Rivaroxaban 10mg is the only NOAC available on the Maltese National Health Service (NHS) formulary and is not available for cardiology patients.

The aim was to compare the NOAC rivaroxaban to warfarin with respect to incidence and severity of bleeding, treatment adherence, drug-drug interactions (DDIs), alcohol consmption and costs.

Following ethics approval, 100 patients (50 warfarin, 50 rivaroxaban) were recruited by convenience sampling from Mater Dei Hospital (MDH) outpatients and from community pharmacies. Bleeding complications were classified according to the Bleeding Academic Research Consortium (BARC) criteria. Medication adherence was assessed using a validated adherence questionnaire. Time in therapeutic range (TTR) for warfarin was calculated using the Rosendaal Linear Interpolation Method. Micromedex® and Medscape® drug interaction checker tools were used to identify potential DDIs. Cost analysis incorporated drug, INR monitoring and physician costs.

For the total population of 100 patients, mean age was 65 ±12.91 (range 27-85) years, 53 were female and 47 were male, the main indications for anticoagulation were atrial fibrillation (59 patients) followed by deep vein thrombosis (30 patients) and mean duration of anticoagulant therapy was 10 ±5.97 (range 1-33) months. Twenty-four patients reported BARC Type 1 bleeding (18 warfarin and 6 rivaroxaban) and 10 patients reported Type 2 bleeding (6 warfarin and 4 rivaroxaban) (p<0.001). Mean adherence

score was 41 ±3.92 (range 30-45) for warfarin and 44 ±1.41 (range 39-45) out of 45 for rivaroxaban (p<0.001). A total of 768 INR tests were processed in a six-month period, with a mean of 2.56 ±1.58 (range 1-7) INR tests per patient per month. Thirty-seven percent of these INR tests were not in therapeutic range. A total of 91 (mean 1.8 ±1.03, range 0-4/patient) and 19 (mean 0.4 ±0.52, range 0-2/patient) potential DDIs were identified in patients on warfarin and rivaroxaban respectively (p<0.001). The mean retail cost/patient/month was €4.20 ±1.63 (range €1.82-€8.46) for patients on warfarin and €97.50 ±0.00 (range €97.50-€97.50) for patients on rivaroxaban

Patients on warfarin 1) had an increased incidence of Type 1 and Type 2 bleeding, 2) were less adherent to treatment, 3) had a lower TTR and 4) had a higher risk of potential DDIs. These factors should be incorporated into a pharmacoeconomic model when justifying the inclusion of rivaroxaban (NOACs) in the NHS formulary for cardiology patients.

Keywords: adherence, bleeding, cost analysis, drug-drug interactions, rivaroxaban, warfarin

Table of Contents

List of Tables

List of Figures

List of Appendices

List of Abbreviations

ACC	Anticoagulation clinic
ACCF	American College of Cardiology Foundation
ACCP	American College of Chest Physicians
ACE-I	Angiotensin converting enzyme inhibitor
AF	Atrial fibrillation
AHA	American Heart Association
ARB	Angiotensin-II receptor blocker
BARC	Bleeding Academic Research Consortium Criteria
BB	Beta-blocker
BD	Twice daily
CCB	Calcium channel blocker
CCS	Canadian Cardiovascular Society
CI	Confidence Interval
CPSU	Central procurement and supplies unit
CYP	Cytochrome P450
DDI	Drug-drug interaction
DVT	Deep vein thrombosis
ECH	Extracranial haemorrhage
EMA	European Medicines Agency
ESC	European Society of Cardiology
FDA	Food and Drug Administration
HRS	Heart Rhythm Society
GI	Gastrointestinal
GUSTO	Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries
ICH	Intracranial haemorrhage
INR	International normalised ratio
MDH	Mater Dei Hospital
MI	Myocardial infarcation
MOP4	Medical Outpatients 4

NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NOAC	Novel Oral Anticoagulant
OD	Once daily
OHA	Oral hypoglycaemic agent
PE	Pulmonary embolism
POC	Point-of-care
PPI	Proton pump inhibitor
QALY	Quality adjusted life years
SD	Standard Deviation
TAQ	Treatment Adherence Questionnaire
TIMI	Thrombolysis In Myocardial Infarction
TTR	Time in therapeutic range
UK	United Kingdom
USA	United States of America
VKORC1	Vitamin K epoxide reductase
VTE	Venous thromboembolism

Chapter 1
Introduction

1.1 Thromboembolic disease and anticoagulation therapy

Arterial and venous thromboembolism, including myocardial infarction (MI), ischaemic and haemorrhagic stroke, deep vein thrombosis (DVT) and pulmonary embolism (PE), are a leading cause of morbidity and mortality, accounting for 1 in 4 deaths worldwide (Lozano et al, 2012; ISTH Steering Committee, 2014; The Lancet Haematology 2015).

Therapeutic intervention with oral and parenteral anticoagulants in stroke, atrial fibrillation (AF), MI, DVT, PE and prosthetic heart valves, prevents and reduces the risk of arterial and venous thrombosis (Raskob et al, 2014; Mekaj et al, 2015). The duration and dosing of anticoagulation depends on the indication, type of anticoagulant used and on external factors such as age, sex and genetic variation (Ageno et al, 2012; Khoury and Sheikh-Taha, 2014). Successful therapeutic use of anticoagulants involves achieving a balance between decreasing the risk of thrombus formation and reducing the risk of bleeding complications (Qiang and Anthony, 2011).

1.2 Oral anticoagulation therapy

Warfarin has been extensively studied, both from a pharmacological and clinical perspective, and has been the gold standard oral anticoagulant for prevention and/or treatment of stroke and thromboembolism in AF and venous thromboembolism (VTE) patients for over 70 years (Wadhera et al, 2014). During the past decade, medical advances in research led to the introduction of novel oral anticoagulants (NOACs) (Ahmad and Lip et al, 2012). Several NOAC compounds have been studied, however the

four compounds that have acquired market approval are dabigatran, rivaroxaban, apixaban and edoxaban (Mekaj et al, 2015).

1.2.1 Anticoagulation therapy with warfarin

Warfarin was discovered by serendipity and its existence dates back to the 1920s. In the 1940s, warfarin was initially used and marketed as a potent rodent poison, however following several studies, its therapeutic use in human medicine was discovered and approved in 1954 (Pirmohamed, 2006; Francis, 2008; Wardrop and Keeling, 2008; Shehab et al, 2016). Warfarin is a vitamin K antagonist, exerting its effect by inhibiting vitamin K-dependent clotting factor production, namely factor VII, IX, X and prothrombin, to prevent thrombus formation (DiPiro et al, 2014).

Warfarin is one of the cheapest life-saving drugs on the market (Zoccai et al, 2013). However, the costs are somewhat debatable since the time and resources allocated for regular INR monitoring and risk of bleeding complications have to be considered (St John and Price, 2013). The clinical and economic outcomes of warfarin are strongly dependent on the quality of anticoagulation monitoring where it has been reported that improved INR control results in a reduction in stroke rates, an increase in quality-adjusted life years and a decrease in costs (Sorensen et al, 2009; Singh, 2012; Lanitis et al, 2014a). Several inexpensive antidotes to reverse the effects of warfarin are available. The most commonly used agent for reversal of warfarin is phytonadione, which exerts its effect through production of vitamin K-dependent clotting factors. Other reversal agents include fresh frozen plasma and clotting factor concentrates (Kalus, 2013).

Factors such as narrow therapeutic index, inter-individual dose response due to genetic variability, other comorbidities and drug and food interactions affect the safety profile of warfarin (Kimmel, 2008; Dyar et al, 2015). Warfarin must be dose titrated to achieve a target INR and is dependent on the patient and indication for use. Evidence has shown difficulty in achieving and maintaining target INR (Kim et al, 2009; Schein et al, 2016).

Pharmacogenomics studies have shown a relationship between cytochrome P450 (CYP) 2C9 and vitamin K epoxide reductase (VKORC1) genes and warfarin dose variability (Pirmohamed et al, 2013; Johnson et al, 2014; Bader and Elewa, 2016). Concomitant administration of CYP inducers, such as cigarette smoking, anticonvulsants and hypoglycaemic agents, and CYP inhibitors, such as protease inhibitors, macrolides and azole antifungals, can affect warfarin levels (Holbrook et al, 2005; Lozano and Franco, 2016). Conditions such as hyperthyroidism, liver disease, congestive heart failure, renal impairment, diarrhoea and fever can increase the anticoagulant effect of warfarin, while hypothyroidism and obesity are associated with a decreased anticoagulant effect (Demirkan et al, 2000; Abdel-Aziz et al, 2015; Self et al, 2016). Consumption of alcohol, cranberry juice and grapefruit juice also affects anticoagulation (Holbrook et al, 2005; Chock et al, 2009; Bushra et al, 2011; Ge et al, 2014). Studies have shown that an enhanced warfarin effect was observed in patients with acute excessive alcohol intake and a reduced warfarin effect was observed in regular heavy drinkers. Cranberry and grapefruit juice are associated with enhanced anticoagulant effect (Holbrook et al, 2005; Chock et al, 2009; Bushra et al, 2011; Ge et al, 2014). A decreased anticoagulant effect is observed when Vitamin-K rich foods, such as green leafy vegetables and liver, are consumed. Food and drug interactions affecting the pharmacokinetic profile of warfarin

may lead to decreased adherence to treatment and need for more frequent INR monitoring (Macedo et al, 2015). In the United States of America (USA), warfarin has been implicated as the most common medication resulting in emergency hospitalisations in the elderly (Budnitz et al, 2011).

1.2.2 Anticoagulation therapy with novel oral anticoagulants

NOACs inhibit thrombin-induced platelet activation and fibrin clot formation through an effect on a single clotting factor, factor IIa or Xa. The mechanism of action of NOACs differs from warfarin in that it antagonises a single target in the coagulation cascade rather than affecting multiple clotting factors (Garcia et al, 2010).

Dabigatran is a direct inhibitor of factor IIa, exerting its effect by inhibiting bound and unbound thrombin and thrombin-induced platelet aggregation (Ageno et al, 2012). Dabigatran (75, 110 and 150mg) gained European Medicines Agency (EMA) and Food and Drug Administration (FDA) approval for stroke prevention in patients with non-valvular AF in 2008 and 2010 respectively. Dabigatran was approved by EMA and FDA for treatment and reduction in risk of recurrent DVT and PE in 2014 (Pottegard et al, 2014; Chan and Pisano, 2015; Baik et al, 2016; Ieko et al, 2016).

Rivaroxaban, apixaban and edoxaban exert their anticoagulation effect by directly inhibiting factor Xa within the coagulation cascade (Ageno et al, 2012). Rivaroxaban (10, 15 and 20mg) and apixaban (2.5 and 5mg) were granted FDA and EMA approval to reduce the risk of stroke and systemic embolism in patients with non-valvular AF in 2008

and 2011 respectively. Approval for treatment and reduction in the risk of recurrent DVT and PE was granted by EMA in 2011 and by the FDA in 2012. Edoxaban (15, 30 and 60mg) was the last NOAC to gain FDA and EMA approval for high-risk patients with non-valvular AF and for treatment and reduction in the risk of recurrent DVT and PE in 2015 (Pottegard et al, 2014; Chan and Pisano, 2015; Baik et al, 2016; Ieko et al, 2016).

Dabigatran, rivaroxaban, apixaban and edoxaban differ in their pharmacokinetic profile with different dosing, bioavailability, renal excretion, liver metabolism and interactions. When recommending a NOAC patient characteristics and preferences should also be considered (Table 1.1).

Table 1.1: Pharmacokinetic profile of novel oral anticoagulants

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Usual dose	150mg bd	20mg od (with food)	5mg bd	60mg od
Bioavailability (%)	3-7	66 (without food); almost 100 (with food)	50	62
Peak plasma level (h)	2	2-4	1-4	1-2
Half-life (h)	12-17	5-9 (young), 11-13 (elderly)	12	10-14
Renal excretion (%)	80	35	27	50
Liver metabolism	No	Yes	Yes	Minimal
Recommendations for NOAC selection	High ischaemic stroke risk, low bleeding risk	CAD, previous MI, high risk for ACS/MI, renal impairment	Previous/high risk of GI bleed, renal impairment, diarrhoea disorders	Previous/high risk of GI bleed, renal impairment

ACS: Acute coronary syndrome; **bd**: twice daily; **CAD**: Coronary artery disease; **GI**: Gastrointestinal; **MI**: Myocardial infarction; **od**: once daily

Adapted from: Connelly D. New oral anticoagulants for stroke prevention in atrial fibrillation. Pharm J. 2016; 297: 7893.

1.2.3 Comparison between warfarin and novel oral anticoagulants

Warfarin is indicated for several medical conditions including prosthetic heart valves, transient ischaemic attack, prophylaxis of systemic embolism in heart disease and AF and for prophylaxis and/or treatment of VTE and PE. The main indications for NOACs are to reduce the risk of stroke and systemic embolism in patients with non-valvular AF

and for treatment and reduction in the risk of recurrent DVT and PE. NOACs are not approved to be used in pregnancy, children and infants (Mekaj et al, 2015). Although no laboratory INR monitoring for NOACs is required, renal and hepatic function tests should be carried out routinely. NOACs are relatively or absolutely contraindicated in patients with severe renal and hepatic impairment. This may be problematic, since the majority of patients taking anticoagulants are geriatric patients in whom renal and hepatic function may deteriorate with increasing age (Vilchez et al, 2014; Mekaj et al, 2015; Khoury et al, 2016). Moreover, NOACs have only recently been introduced and there is limited evidence on their long-term effects (Mekaj et al, 2015). Dabigatran is the only NOAC that has an approved reversal agent available on the market. Idarucizumab has demonstrated complete reversal of the effect of dabigatran and was granted approval in 2015 (Bauer, 2013; Chu et al, 2015; Das and Liu, 2015; Pollack et al, 2015). NOACs present a significantly higher retail cost compared to warfarin, since they are still on patent and no generic drug is currently available (Hanley and Kowey, 2014).

Due to a more predictable pharmacological profile, NOACs have a fixed dosing regimen and require no INR monitoring (Shehab et al, 2016). Compared to warfarin, NOACs have a quicker onset/offset of action, where rapid onset eliminates the need for initial treatment with a parenteral anticoagulant and rapid offset is important in cases of surgical intervention (Bauer, 2013; Mekaj et al, 2015). NOACs have considerably less drug-drug interactions (DDIs) and impact less on dietary restrictions imposed on the patient compared to warfarin. To date fewer DDIs with NOACs when compared to warfarin have been observed (Bauer, 2013; Mohrein et al, 2013; Mekaj et al, 2015; Amin,

2016; Raval et al, 2017). The advantages of NOACs have shown an increase in patient adherence to treatment (Biskupiak et al, 2013).

1.3 Effectiveness and safety of novel oral anticoagulants

The efficacy and safety of NOACs in non-valvular AF and VTE have been extensively studied in various clinical trials.

1.3.1 Stroke prevention in non-valvular atrial fibrillation

There are four pivotal clinical trials, RE-LY, ROCKET-AF, ARISTOTLE and ENGAGE AF-TIMI 48, comparing NOACs to warfarin in patients with non-valvular AF. The RE-LY trial (Connolly et al, 2009) compared dabigatran 110mg and dabigatran 150mg to warfarin and showed that the 150mg dose was significantly superior ($p<0.001$) to warfarin in preventing systemic embolism and stroke. Major bleeding rates were significantly lower ($p<0.05$) with the 110mg dose and lower, but not significantly ($p>0.05$), with the 150mg dose. A follow-up two-year extension trial, RELY-ABLE (Connolly et al, 2013), compared outcomes between both dabigatran doses, showing similar rates of stroke and death and an increased risk of major bleeding with dabigatran 150mg.

The ROCKET-AF trial (Patel et al, 2011) compared a fixed dose of rivaroxaban, 20mg or 15mg daily depending on creatinine clearance, with warfarin in patients with nonvalvular AF. Rivaroxaban was significantly non-inferior to warfarin in the prevention of systemic embolism and stroke ($p<0.001$), however there was no significant difference

in major bleeding rates between rivaroxaban and warfarin ($p > 0.05$). Validity of the ROCKET-AF trial was debated when findings indicating use of a faulty point-of-care (POC) device to measure INR in patients taking warfarin was discovered (Cohen, 2016a,b). Researchers of the ROCKET-AF trial disputed claims that the faulty INR monitoring device had an impact on the results and published a series of post-hoc analyses of the ROCKET-AF data (Patel and Hellkamp, 2016). Analyses carried out by the FDA also concluded that the ROCKET-AF results were not affected by the faulty monitoring device, hence reaffirming the safety and efficacy profile of rivaroxaban.[1]

The ARISTOTLE trial (Granger et al, 2011) compared apixaban 5mg twice daily to warfarin in patients with non-valvular AF and a single risk factor for stroke. Apixaban was significantly superior to warfarin in the prevention of systemic embolism and stroke ($p < 0.05$) and major bleeding rates were significantly lower ($p < 0.001$) in the apixaban cohort.

The ENGAGE AF-TIMI 48 trial (Giugliano et al, 2013) was the largest trial conducted in non-valvular AF patients comparing edoxaban 30mg and 60mg to warfarin. Both doses of edoxaban were significantly non-inferior to warfarin in the prevention of systemic embolism and stroke ($p < 0.05$). Major bleeding rates were significantly lower ($p < 0.001$) in both edoxaban cohorts compared to warfarin. A comparison of the four trials in non-valvular AF is summarised in Table 1.2.

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[1]FDA. FDA analyses conclude that Xarelto clinical trial results were not affected by faulty monitoring device [Online]. USA: FDA; 2016 [cited 2017 Jun 12]. Available from: URL: http://www.fda.gov/Drugs/DrugSafety/ucm524678.htm.

Table 1.2: Comparison of clinical trials in non-valvular atrial fibrillation

Trial	% Event rate/year p-value					
	Stroke and Systemic Embolism	Ischaemic Stroke	Haemorrhagic Stroke	Major Bleeding	Intracranial Bleeding	Gastrointestinal Bleeding
RE-LY[a] (N=18,113)						
Warfarin (n=6022)	1.72	1.22	0.38	3.61	0.77	1.09
Dabigatran 150mg (n=6076)	1.12 p<0.001 SUPR	0.93 p=0.030	0.10 p<0.001	3.40 p=0.410	0.32 p<0.001	1.60 p<0.001
Dabigatran 110mg (n=6015)	1.54 p<0.001 NI	1.34 p=0.420	0.12 p<0.001	2.92 p=0.003	0.23 p<0.001	1.13 p=0.740
ROCKET-AF[b] (N=14,264)						
Warfarin (n=7133)	2.40	1.42	0.44	3.45	0.74	1.24
Rivaroxaban 20mg (n=7131)	2.10 p<0.001 NI	1.34 p=0.581	0.26 p=0.024	3.60 p=0.580	0.49 p=0.020	2.00 p<0.001
ARISTOTLE[c] (N=18,201)						
Warfarin (n=9081)	1.60	1.05	0.47	3.09	0.80	0.86
Apixaban 5mg (n=9120)	1.27 p<0.001 NI p=0.01 SUPR	0.97 p=0.420	0.24 p<0.001	2.13 p<0.001	0.33 p<0.001	0.76 p=0.370
ENGAGE AF-TIMI 48[d] (N=21,105)						
Warfarin (n=7036)	1.80	1.25	0.47	3.43	0.85	1.23
Edoxaban 30mg (n=7035)	2.04 p=0.005 NI	1.77 p<0.001	0.16 p<0.001	1.61 p<0.001	0.26 p<0.001	0.82 p<0.001
Edoxaban 60mg (n=7035)	1.57 p<0.001 NI	1.25 p=0.970	0.26 p<0.001	2.75 p<0.001	0.39 p<0.001	1.51 p=0.030

NI = Non-Inferiority; SUPR = Superiority

Adapted from:

a. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, ldgren J, Parekh A et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009; 361: 1139-51.

b. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011; 365(10): 883-91.

c. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011; 365: 981-92.

d. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013; 369: 2093-104.

Smaller-scale studies (Graham et al, 2016; Kwon et al, 2016; Larsen et al, 2016; Noseworthy et al, 2016; Yao et al, 2016) reported similar results to the major trials in terms of stroke and systemic embolism rates compared to warfarin.

As regards bleeding, studies have shown that in patients taking a NOAC, bleeding rates are comparable or lower than in patients receiving warfarin. Lip et al. (2016b) showed no significant difference ($p>0.05$) in major bleeding risk in patients taking rivaroxaban compared to warfarin, whereas patients on apixaban and dabigatran had a statistically significant ($p<0.05$) lower risk of major bleeding compared to warfarin. Similar results were reported in other studies, showing comparable bleeding rates for warfarin and rivaroxaban, which were higher than with apixaban and dabigatran (Larsen et al, 2016; Yao et al, 2016; Halvorsen et al, 2017).

1.3.2 Venous thromboembolism

There are five major clinical trials, RE-COVER, EINSTEIN-DVT, EINSTEIN-PE, AMPLIFY and Hokusai-VTE, comparing NOACs to warfarin in patients with DVT and PE. The RE-COVER trial (Schulman et al, 2009) compared dabigatran 150mg twice daily to dose-adjusted warfarin and showed that dabigatran was significantly non-inferior to warfarin in preventing recurrent VTE ($p<0.001$). Major bleeding rates between dabigatran and warfarin were comparable ($p>0.05$). A replica study, RE-COVER II (Schulman et al, 2014), confirmed the results of the RE-COVER trial by concluding similar efficacy endpoints and bleeding outcomes. The RE-MEDY (dabigatran 150mg twice daily versus warfarin) and RE-SONATE (dabigatran 150mg twice daily versus placebo) trials compared use of

dabigatran for the secondary prevention of DVT (Schulman et al, 2013), where dabigatran was significantly superior compared to placebo (p<0.001) and to warfarin (p<0.05). Major or clinically relevant bleeding events were significantly lower for dabigatran compared to warfarin (p<0.001) and significantly higher for dabigatran compared to placebo (p<0.05).

The EINSTEIN-DVT and EINSTEIN-PE trials (Bauersachs et al, 2010; Buller et al, 2012) compared rivaroxaban 15mg twice daily for three weeks, followed by 20mg once daily to enoxaparin/warfarin in DVT and PE. Rivaroxaban was significantly non-inferior to enoxaparin/warfarin (p<0.001 in DVT; p<0.05 in PE) in the prevention of recurrent VTE. There was no statistical difference in major or clinically non major bleeding between rivaroxaban and enoxaparin/warfarin in DVT and PE patients (p>0.05). EINSTEIN Extension (Romualdi et al, 2011) was a follow-up trial, where randomly assigned patients received continued treatment with rivaroxaban or placebo. Rivaroxaban significantly decreased the risk of recurrent VTE compared to placebo (p<0.001) and major bleeding rates were significantly higher for the rivaroxaban group compared to placebo (p<0.001).

The AMPLIFY trial (Agnelli et al, 2013) showed that apixaban 10mg twice daily for seven days, followed by apixaban 5mg once daily was significantly non-inferior to enoxaparin/warfarin in preventing recurrent VTE (p<0.001). Major bleeding rates were significantly lower for the apixaban group compared to warfarin (p<0.001). The AMPLIFY-extension trial (Agnelli et al, 2013) compared apixaban 2.5mg and apixaban 5mg to placebo in secondary prevention of recurrent VTE. Both apixaban doses significantly decreased the risk of recurrent VTE compared to placebo (p<0.001). Major

bleeding rates were non-significantly higher in the placebo group compared to both doses of apixaban (p>0.05).

The Hokusai-VTE trial (Buller et al, 2013) compared edoxaban to a fixed dose of rivaroxaban, 20mg or 15mg daily depending on creatinine clearance, with warfarin for treatment of symptomatic VTE. Edoxaban was significantly non-inferior to warfarin in preventing recurrent VTE (p<0.001) and major bleeding rates were non-significantly lower for edoxaban compared to warfarin (p>0.05). A comparison of the five trials in VTE are summarised in Table 1.3.

Table 1.3: Comparison of clinical trials in venous thromboembolism

Trial	% Event rate/year p-value		
	Recurrent VTE or VTE-related death	**Major Bleeding**	**Major or clinically relevant nonmajor bleeding**
RE-COVER [a] (N=2,539)			
Warfarin (n=1265)	2.1	1.9	8.8
Dabigatran 150mg (n=1274)	2.4 p<0.001 NI	1.6 p=0.26	5.6 p=0.002
EINSTEIN-DVT [b] (N=3,449)			
Enoxaparin/Warfarin (n=1718)	3.0	1.2	8.1
Rivaroxaban 15/20mg (n=1731)	2.1 p<0.001 NI	0.8 p=0.21	8.1 p=0.77
EINSTEIN-PE [c] (N=4,832)			
Enoxaparin/Warfarin (n=2413)	1.8	2.2	11.4
Rivaroxaban 15/20mg (n=2419)	2.1 p=0.003 NI	1.1 p=0.003	10.3 p=0.23
AMPLIFY [d] (N=5,395)			
Enoxaparin/Warfarin (n=2635)	2.7	1.8	9.7
Apixaban 10/5mg (n=2609)	2.3 p<0.001 NI	0.6 p<0.001	4.3 p<0.001
Hokusai-VTE [e] (N=8,292)			
Enoxaparin/Warfarin (n=4122)	3.2	1.6	10.3
Edoxaban 30/60mg (n=4118)	3.5 p<0.001 NI	1.4 p=0.35	8.5 p=0.004

NI = Non-Inferiority, VTE

Adapted from:

a. Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H et al. Dabigatran vs warfarin in the treatment of acute venous thromboembolism. N Engl J Med. 2009; 361(24): 2342-52.

b. Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, Gallus AS. Oral Xa for symptomatic venous thromboembolism. N Engl J Med. 2010; 363(26): 2499-510.

c. Buller HR, Prins MH, Lensing AWA, Decousus H, Jacobson BF, Minar E et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med. 2012; 366: 1287-97.

d. Buller HR, Decousus H, Grosso MA, Mercuri M, Middledrop S, Prins MH et al. Edoxaban vs warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med. 2013. 369: 1406-15.

e. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M et al; AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med. 2013; 369: 799-808.

1.4 Comparative effectiveness of novel oral anticoagulants

Head-to-head trials comparing NOACs could potentially generate influential comparative evidence (Flacco et al, 2015). To-date, no head-to-head trial comparing NOACs has been conducted due to the financial burden and time constraints imposed on manufacturers (Karamichalakis et al, 2016). As a result, pharmacological and economic analysis are based on network meta-analysis (NMAs), which analyse available direct and indirect evidence to estimate relative treatment effectiveness between NOACs (Cohen et al, 2015). NMAs are important in the formulation of guidelines as they reduce bias, strengthen evidence and provide a more concise assessment, leading to improved decision-making (Kanters et al, 2016). Numerous NMAs comparing NOACs have been conducted to assess the safety and efficacy of such interventions (Lip et al, 2012; Schneeweiss et al, 2012; Zoccai et al, 2013; Ruff et al, 2014; Cohen et al, 2015; Vedovati et al, 2015; Vallakati et al, 2016). The results from NMAs are highly variable, depending on the inclusion and exclusion criteria and type of statistical model used. Results from clinical trials and other post-hoc studies are important in the development of relevant, up-to-date guidelines.

1.5 Current therapy guidelines for oral anticoagulation

Guidelines for the use of oral anticoagulants weigh the likelihood of stroke with the increased risk of bleeding (Amin, 2013; Ment, 2015). USA, Canada, United Kingdom (UK) and European guidelines have been updated over the past few years to recommend use of NOACs as an alternative to warfarin for stroke prevention in patients with non-

valvular AF and in PE and in the secondary prevention of VTE. The American College of Cardiology Foundation (ACCF), the American Heart Association (AHA), the Heart Rhythm Society (HRS), the Canadian Cardiovascular Society (CCS) and the European Society of Cardiology (ESC) guidelines state that stroke risk in non-valvular AF and VTE should be estimated based on the number of CHA_2DS_2-VASc risk factors (January et al, 2014; Heidbuchel et al, 2015; Kirchhof et al, 2016). This index broadens the spectrum in classifying patients with low stroke risk. Patients with a CHA_2DS_2-VASc score of 0 theoretically require no antithrombotic therapy. Males with a CHA_2DS_2-VASc score of 1 and females with a CHA_2DS_2-VASc score of 2 should be prescribed oral anticoagulation, whilst balancing bleeding risk, reduction in stroke and patient preference (January et al, 2014; Kirchhof et al, 2016). In addition to stroke risk, bleeding risk should also be considered when prescribing the appropriate oral anticoagulant. The HAS-BLED Index has been validated and proven to be superior to other bleeding indices such as ATRIA and $HEMORR_2HAGES$ (Lip et al, 2011). The ESC guidelines are the only guideline that combine the CHA_2DS_2-VASc and HAS-BLED indices (Kirchhof et al, 2016).

The ACCF, AHA and HRS guidelines recommend either warfarin or a NOAC in patients with non-valvular AF (January et al, 2014). Selection is individualised to every patient depending on cost, tolerability, risk factors, potential DDIs and patient preference, amongst other clinical factors. The National Institute for Health and Care Excellence (NICE) guidelines also recommend the NOACs dabigatran, rivaroxaban and apixaban as an alternative to warfarin in non-valvular AF in patients with previous stroke or transient ischaemic attack, ≥75 years, heart failure, diabetes or hypertension. ESC and CCS

guidelines prefer NOACs over warfarin in patients with non-valvular AF (Kirchhof et al, 2016; Macle et al, 2016).

In 2014, the ESC issued guideline recommendations on the use of anticoagulants in DVT and PE. These guidelines suggest that NOACs can be used as alternatives to warfarin both in the acute and long-term treatment of VTE (Konstantinides et al, 2014). The most recent guidelines on antithrombotic therapy for DVT and PE, published in 2016 by the American College of Chest Physicians (ACCP) (Kearon et al, 2016), recommend use of a NOAC over warfarin in patients with DVT or PE and no cancer for the first three months of treatment. In patients with cancer-associated thrombosis, low molecular weight heparin is preferred to warfarin and NOACs for the first three months of treatment. Patients who require continued treatment with an anticoagulant beyond three months can remain on the initial treatment. The ACCP guidelines also recommend treatment durations depending on the type of VTE, namely provoked or unprovoked. Anticoagulant therapy for unprovoked VTE in cancer patients with low to moderate bleeding risk should be extended. Anticoagulant therapy in unprovoked VTE in high bleeding risk patients should be stopped after three months (Kearon et al, 2016).

1.6 Pharmacoeconomic studies of oral anticoagulants

Pharmacoeconomics describes and analyses the costs and consequences of pharmaceutical services and products and their effect on health care systems, individuals and society. Pharmacoeconomics plays a vital role when assessing therapeutic drug monitoring, biotechnology drugs and disease management (Reddy et al, 2008).

The cost-effectiveness of NOACs depends on the setting, indication for anticoagulation and cost of anticoagulant care services. Markov models are the most commonly used models when carrying out cost-effectiveness analysis. Markov models incorporate disease, treatment progress, effect on Quality-adjusted life-years (QALYs) and costs to society (Abler et al, 2013). The results obtained are highly dependent on the data inputted in the Markov model.

Several pharmacoeconomic analyses using data from clinical trials have been conducted to compare the cost-effectiveness of a single NOAC to warfarin in patients with non-valvular AF. Studies comparing cost-effectiveness of dabigatran to warfarin in a USA (Shah et al, 2011; Clemens et al, 2014), UK (Kansal et al, 2012) and European (Galvani et al, 2015) setting indicated that dabigatran is a cost-effective option to warfarin in non-valvular AF. Studies comparing rivaroxaban to warfarin in non-valvular AF showed that rivaroxaban is a cost-effective option in Belgium (Kleintjens et al, 2013), Greece (Kourlaba et al, 2014), Germany (Mensch et al, 2015) and Japan (Hori et al, 2016). Apixaban was also shown to be a cost-effective option compared to warfarin in patients with non-valvular AF in a USA (Kamel et al, 2012a), UK (Dorian et al, 2014) and European

(Pinyol et al, 2016) setting. Studies in Germany (Krejczy et al, 2015), Italy (Rognoni et al, 2015), and the USA (Magnuson et al, 2015; Nguyen et al, 2016) showed that edoxaban was cost-effective compared to warfarin for stroke prevention in non-valvular AF.

Cost-effective analyses comparing dabigatran, rivaroxaban, apixaban and edoxaban to warfarin in patients with non-valvular AF have also been conducted. Results indicate that in the majority of Markov models, NOACs were cost-effective options compared to warfarin (Krejczy et al, 2014; Zheng et al, 2014; Janzic and Kos, 2015; Liu and Chen, 2017).

Fewer studies comparing NOACs to warfarin in patients with VTE have been conducted. These studies reported that dabigatran (Stevanovic et al, 2016), rivaroxaban (Baugh et al, 2016) and apixaban (Lanitis et al, 2017) are cost-effective compared to warfarin in VTE, in the Netherlands, USA and UK respectively.

To-date no pharmacoeconomic studies comparing warfarin and NOACs have been undertaken in Malta.

1.7 Situation in Malta

At the time of the study, warfarin was the only oral anticoagulant available on the Maltese Government Formulary List (GFL). Rivaroxaban 10mg was the only NOAC available on the GFL indicated for prevention of VTE in adult patients after hip or knee replacement surgery and not for cardiology patients. Three NOACs were available on

the private retail market in Malta; dabigatran (Pradaxa®), rivaroxaban (Xarelto®) and apixaban (Eliquis®). Edoxaban was not yet available in Malta (Table 1.4).

Table 1.4: Date of issue of NOAC marketing authorisation in Malta

Novel Oral Anticoagulant	Date of Authorisation
Dabigatran	March 18, 2008
Rivaroxaban	September 30, 2008
Apixaban	May 18, 2011

When introducing any new treatment in Malta, the Central Procurement and Supplies Unit (CPSU) is faced with the challenge to decide whether, the benefit of a treatment warrants its added cost. In 2016, government spending in the healthcare sector increased by 12.5%, with an expected increase by another 11.4% in 2017.[2] Cost containment measures must be implemented to safeguard and ensure that the system remains sustainable. Economic evidence is vital to provide the best evidence when considering introduction of a new treatment in the GFL.

In Malta, patients taking warfarin have their INR checked at the Anticoagulation Clinic (ACC) at Mater Dei Hospital (MDH) with a laboratory-based method using a venous blood sample, or at a health care centre by means of POC testing from a finger-prick blood sample. Both services are provided by the Maltese national health service (NHS) free-of-charge.

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[2] The Malta Independent. Report praises progress in health care sector but obesity still massive problem [Online]. Malta; 2017 [cited 2017 Jun 12]. Available from: URL: http://www.independent.com.mt/articles/2017-02-28/local-news/Report-praises-progress-in-health-sector-but-obesity-still-massive-problem-6736171050.

Patients who start taking warfarin are referred directly by their physician to the ACC clinic. For the first three visits the patient must always attend the ACC clinic for monitoring. Following these three appointments, the patient may opt to start checking the INR at the respective health care centre. It usually takes up to three to four hours for the INR results to become available. Patients attending a follow-up appointment are sent home after their blood sample is taken and their INR value and dose prescription is sent by postal mail. Patients with altered INR results and who require a change in dose are contacted by the ACC via telephone, usually on the same day of their appointment or the morning after.

The POC INR testing service started operating in health care centres in 2014. With this system, the patients are given the INR result and warfarin prescription within minutes. This system also allows face-to-face discussion of the INR result and dose with the physician and reduces waiting time and overcrowding at the ACC. This approach may lead to a decrease in dose/administrative errors which may occur when INR results and dose are communicated via telephone. Moreover, POC testing requires a smaller amount of blood, obtained via a finger prick test, making the procedure less invasive compared to a venous blood sample.

Regular renal function tests in patients taking NOACs should be carried out at least yearly (Chin, 2016). In Malta, no protocol exists at MDH stipulating regular renal fuction monitoring every six months or yearly.

1.8 Rationale for the research

Vitamin K antagonists have been the mainstay drugs for the treatment and prevention of thromboembolism for over 50 years. Limitations of warfarin include a narrow therapeutic index, inter-individual dose response due to various factors, need for frequent INR monitoring and numerous drug and food interactions. Dabigatran, rivaroxaban and apixaban are available on the Maltese market. NOACs have similar or superior safety and efficacy profiles to warfarin, however require no INR monitoring due to their more predictable pharmacological profile. This study will help to determine, bleeding complications, adherence rates, INR control, DDIs and costs between warfarin and rivaroxaban.

1.9 Aim and objectives

The aim was to compare the NOAC rivaroxaban to warfarin with respect to incidence and severity of bleeding, medication adherence, drug-drug interactions and costs.

The objectives were to:

I.   Determine differences in patient characteristics between patients taking rivaroxaban and warfarin.

II. Compare incidence and severity of ischaemic outcomes and bleeding complications between patients taking rivaroxaban and warfarin

III. Determine and compare patient adherence to rivaroxaban and warfarin

IV. Assess and evaluate INR control in patients on warfarin

V.   Identify drug-drug interactions in patients taking rivaroxaban and warfarin

VI.   Carry out a cost analysis of rivaroxaban with warfarin by incorporating drug, monitoring and physician costs

VII. Discuss recommendations in national pharmaceutical policies regarding oral anticoagulation.

Chapter 2
Methodology

The methodology included development and validation of a patient data collection form, ethics approval, a preliminary study to identify NOAC for direct comparison with warfarin, a pilot study to test applicability and practicality of study design and data collection form, recruitment of 100 patients (50 on warfarin/50 on rivaroxaban) according to established inclusion criteria, analysis and interpretation of results, and discussion of recommendations in national pharmaceutical policies regarding oral anticoagulation (Figure 2.1).

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│   Development of patient consent form,   │
│ information sheet and data collection form│
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│     Validation of data collection form   │
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│   Preliminary study to identify NOAC for │
│        direct comparison with warfarin   │
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│       Pilot study and patient recruitment│
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│ Semi-structured interview to assess      │
│ bleeding, adherence, INR control, DDIs   │
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│     Cost analysis and statistical analysis│
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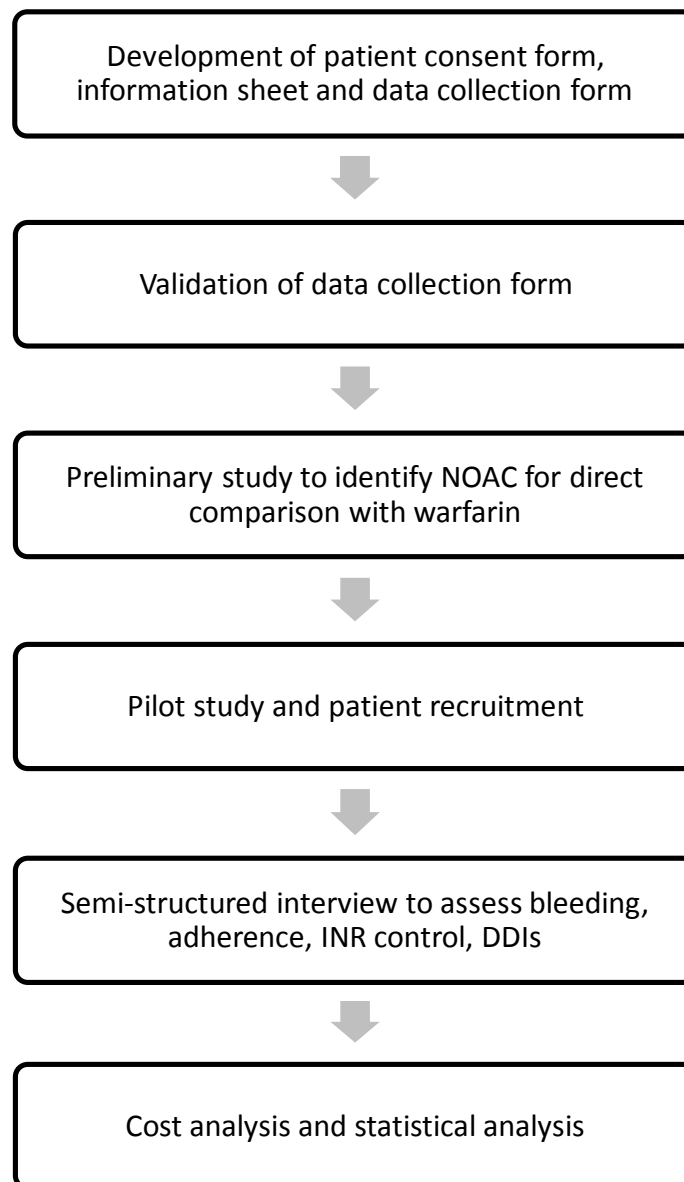
Figure 2.1: Study design flowchart

2.1 Study setting

The study was carried out at the ACC and Department of Cardiology medical outpatients 4 (MOP4) at MDH. Opening hours at the ACC clinic are Monday to Friday from 7:30 am to 2:30 pm and on Saturdays from 7:30 am to 12:00 pm. Opening hours of MOP4 are Monday to Friday from 7:00 am to 3:30 pm and on Saturdays from 7:00 am to 12:00 pm.

Eleven community pharmacies were selected from the six districts in Malta, namely Southern Harbour (Valletta), Northern Harbour (Qormi and St. Julians), South Eastern (Gudja and Għaxaq), Western (Attard and Rabat), Northern (Mosta and Naxxar) and Gozo (Victoria and Xagħra).

2.2 Development of data collection form

A data collection form to document patient data consisting of five sections (A-E) was developed. Table 2.1 shows the layout and content of the data collection form. The data collection form was developed to be completed by the researcher as a semi-structured patient interview. Semi-structured interviews provide reliable, qualitative data, encourage two-way communication and provides opportunity for learning. Semi-structured interviews may be time-consuming and resource intensive and must be carefully planned so as not to pose leading or perceptive questions (Jamshed, 2014).

Table 2.1: Layout and content of data collection form

Section (Question)	Title	Description
A (1-10)	**Patient Details**	Patient study number, telephone/mobile number, gender, age, supervising consultant physician, place of patient recruitment, level of education, living situation, smoking, alcohol consumption
B (11-19)	**Current Anticoagulation Therapy**	Prescribed anticoagulant, dosage and frequency of anticoagulation therapy, indication for anticoagulation therapy, start date of anticoagulant, option to take NOAC instead of warfarin, prior knowledge about NOACs, monitoring of INR, inconvenience of regular INR monitoring, INR results
C (20-26)	**History of Anticoagulation Therapy**	Complications since treatment initiation, emergency admissions to hospital related to anticoagulation therapy, length of stay in hospital related to anticoagulation therapy, visits to GP related to anticoagulation therapy, adverse-effects related to anticoagulation therapy, incidence and severity of bleeding related to anticoagulation therapy
D (27)	**Current Medications**	List of current medications (generic name, dosage strength, dosage regimen)
E (i-ix)	**Adherence to Anticoagulation Therapy**	Nine questions to assess adherence to anticoagulation therapy

Various bleeding classifications such as the Thrombolysis In Myocardial Infarction (TIMI), Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO), PLATO and Bleeding Academic Research Consortium (BARC) criteria have been used in cardiovascular clinical trials (Mehran et al, 2011).

The BARC criteria have been used in studies involving anticoagulants and have demonstrated to be a standardised bleeding classification for patients receiving antithrombotic therapy (Fiedler et al, 2015; Sinigoj et al, 2015; Wang et al, 2016). The BARC criteria classify bleeding, ranging from Type 0 (No bleeding) to Type 5 (Fatal

bleeding) (Table 2.2). The BARC criteria were selected and incorporated into section C

of the data collection form to classify severity of bleeding.

Table 2.2: Bleeding Academic Research Consortium criteria

Type	Definition
0	No Bleeding
1	Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalisation, or treatment by a healthcare professional. May include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional
2	Any overt, actionable sign of haemorrhage (eg. more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3,4 or 5but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalisation or increased level of care, or (3) prompting evaluation
3a	Overt bleeding plus haemoglobin drop of 3 to <5 g/dL (provided haemoglobin drop is related to bleed) Any transfusion with overt bleeding
3b	Overt bleeding plus haemoglobin drop ≥5 g/dL (provided haemoglobin drop is related to bleed) Cardiac tamponade Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/haemorrhoid) Bleeding requiring intravenous vasoactive agents
3c	Intracranial haemorrhage (does not include microbleeds or haemorrhagic transformation, does include intraspinal) Subcategories confirmed by autopsy or imaging or lumbar puncture Intraocular bleed comprising vision
4	CABG-related bleeding Perioperative intracranial bleeding within 48h Reoperation after closure of sternotomy for the purpose of controlling bleeding Transfusion of ≥5 U whole blood or packed red blood cells within 48h Chest tube output ≥2L within a 24-h period
5a	Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious
5b	Definite fatal bleeding; overt bleeding, autopsy, imaging confirmation

Adopted from: Mehran R, Rao SV, Bhatt DL, Gibson M, Caixeta A, Eikelboom J et al. Standardized Bleeding Definitions for Cardiovascular Clinical Trials. A Consensus Report From the Bleeding Academic Research Consortium. Circulation. 2011; 123: 2736-47.

The 20-item treatment adherence questionnaire (TAQ) developed by Anastasi et al. (2017) was adapted to be used in this study to assess adherence to anticoagulation therapy. The TAQ is divided into two parts (A and B), each consisting of 10 questions. Part A uses a 6-point Likert Scale (0 never and 5 always) and Part B uses a 6-point Likert Scale (0 always and 5 never). The maximum total score in the TAQ is 100; the higher the score, the higher the level of adherence to treatment.

Nine of the 20 questions in the TAQ were used to assess medication adherence in this study, with a maximum total score of 45, where the higher the score, the higher the level of adherence (Table 2.3). Three questions were adapted from Part A and six questions were adapted from Part B of the TAQ. The order of questions was kept the same as in the TAQ.

Table 2.3: Adherence questionnaire

Question	Never	Rarely	Occasionally	Sometimes	Often	Always
1. Do you take your prescribed warfarin/rivaroxaban?	0	1	2	3	4	5
2. Do you take warfarin/rivaroxaban at their prescribed times?	0	1	2	3	4	5
3. If you travel abroad, do you take along warfarin/rivaroxaban?	0	1	2	3	4	5
4. Were there any occasions were you stopped taking warfarin/rivaroxaban out of your own free will?	5	4	3	2	1	0
5. Did you ever miss a dose?	5	4	3	2	1	0
6. Did you miss/stop treatment because you forgot?	5	4	3	2	1	0
7. Did you miss/stop treatment because you experienced adverse effects?	5	4	3	2	1	0
8. Did you miss/stop warfarin/rivaroxaban because you have too many medicines and you got confused on how they should be administered?	5	4	3	2	1	0
9. Did you miss/stop treatment, because you felt good and decided that you did not need the medicine?	5	4	3	2	1	0

Adapted from: Anastasi A, Grech L, Serracino Inglott A, Azzopardi LM. CP-185. An innovative treatment adherence tool. Eur J Hosp Pharm. 2017; 24: A83.

2.2 Validation of data collection form

The data collection form was validated by a panel of ten experts to assess relevance of each section/question in the form and level of agreement with the options given. The panel consisted of an equal number of male and female reviewers divided as follows: Two consultant cardiologists, one consultant neurologist, one general practitioner, two hospital pharmacists, two community pharmacists and two lay persons. A form for the validation exercise was developed (Appendix 1). An email giving a brief overview of the study, together with the draft data collection form and validation form, was sent to all members of the validation panel. The validation panel was informed that the form was to be completed by the researcher via a semi-structured patient interview and viewing of hospital-related documentation and was not to be self-administered by the patient. The panel members were given two weeks to validate the form and suggest any amendments.

For each question, each panel member had to assign a score (1 lowest and 5 highest) for relevance and agreement with the options given. The scores were inputted into Microsoft® Excel® 2013 and a mean score for each question (out of 5) was calculated. For relevance, mean rating scores ranged from 3.9 to 5, out of 5 and for level of agreement, mean rating scores ranged from 3.7 to 5, out of 5 (Appendix 2). Questions obtaining a mean score less than 4 were reviewed and amended according to the suggestions proposed by the panel.

Following validation, addition of 'Antiphospholipid Syndrome' was added as an indication for anticoagulation in question 13 and period of INR results to be recorded

was specified as 6 months in question 19 of the data collection form. The final version of the patient data collection form is found in Appendix 3.

2.3 Study approvals

Approval from the Chief Executive Officer, Data Protection Officer, Chairman of the Department of Pathology, Chairman of the Department of Cardiology, Lead Anticoagulation Services, Lead Emergency Department and Consultant Cardiologists at MDH was obtained. Approval from the eleven community pharmacy owners/managing pharmacists participating in the study was obtained. A patient consent form (Appendix 4) and patient information sheet (Appendix 5) were developed in both English and Maltese language. Approvals, patient consent form and patient information leaflet were submitted to the Faculty of Medicine and Surgery Research Ethics Committee for review. University Research Ethics Committee approval was granted, Protocol Number 19/2016 (Appendix 6).

2.4 Preliminary study

A preliminary study was carried out on 50 patients to identify the most commonly prescribed NOAC. The 50 patients were recruited from community pharmacies and MOP4. Thirty patients were taking warfarin, 27 patients were on rivaroxaban, two patients were on dabigatran and one patient was taking apixaban. Rivaroxaban was the most prescribed NOAC and selected to be compared to warfarin.

2.5 Patient recruitment and pilot study

One hundred patients, 50 from MDH outpatients (ACC and MOP4) and 50 from community pharmacies were recruited by convenience sampling according to established inclusion criteria. Patients had to be ≥ 18 years, taking an anticoagulant for ≤ 3 years, suffering from no cognitive impairment and no chronic kidney or liver disease. The patient cohort was divided equally between patients on warfarin (50) and patients on rivaroxaban (50) (Table 2.4).

Table 2.4: Patient recruitment (N=100)

			Anticoagulant	
			Warfarin (n=50)	Rivaroxaban (n=50)
Patient Recruitment	Community Pharmacy	Number of Patients	19	31
	Cardiac Outpatients	Number of Patients	4	19
	Anticoagulation Clinic	Number of Patients	27	0

Patients were interviewed face-to-face by a semi-structured interview technique. The researcher explained the purpose and details of the study and what patient involvement entails. Information was provided verbally and using the patient information leaflet. If the patient agreed to participate in the study, s/he was asked to provide written informed consent by signing the patient consent form. The researcher explained that patient identity will be kept strictly confidential and that the information obtained will only be used for the purpose of the study. Patients were informed that they could withdraw from the study at any time and this would not influence the care and

treatment normally received. Each patient recruited was given a consecutive study number used solely by the researcher to ensure patient confidentiality. The patient's identity card number and name were kept separately by the researcher. The data collection form was completed by the researcher for each patient recruited. Section A and E were completed via patient interview, Section B and C by patient interview and viewing of patient hospital-related documentation and Section D using patient hospital-related documentation. Patient recruitment was carried out between July 1 and December 31, 2016.

A pilot study on 20 patients was carried out to assess the applicability and practicality of the study design and data collection form. No changes were made following the pilot study which was carried out over a two-month period, between May 1 and June 31, 2016.

2.6 Determination of time in therapeutic range

Methods to evaluate time in therapeutic range (TTR) for patients on warfarin were assessed and analysed. The three most common methods include: 1) Calculating fraction of INRs, 2) taking a cross-section-of-the-files method and 3) the Rosendaal linear interpolation method (Rosendaal et al, 1993; Erkens et al, 2012; Singer et al. 2015). The Rosendaal linear interpolation method was selected for use in this study since actual days in target range and INR specific incidence rates of adverse effects are calculated. A comparison between methods is summarised in Table 2.5.

Table 2.5: Comparison of methods to measure time in therapeutic range

Methodology	Advantages	Disadvantages
Fraction of INRs	Simple to calculate Requires only one INR value per patient in population Not influenced by extent of INR out-of-range	More frequent testing in unstable patients may bias overall results Does not take into account actual days within target range Does not consider individual patients
Cross section of the files	Simple to calculate Considers individual patients Not influenced by extent of INR out-of-range	Does not take into account actual days within target range Only considers one point in time
Rosendaal linear interpolation	Takes into account actual days in target range Allows one to calculate INR specific incidence rates of adverse events	Calculation more difficult Makes assumptions about INR between actual tests Does not consider individual patients Extreme out-of-range INR values may bias overall results

Adopted from: Schmitt L, Speckman J, Ansell J. Quality assessment of anticoagulation dose management: comparative evaluation of measures of time-in-therapeutic range. J Thromb Thrombolysis. 2003; 15(3): 213-6.

INR results documented in Section B of the data collection form were used to calculate TTR. The results were inputted in a Rosendaal liner interpolation template which mathematically calculates the percentage days within range and percentage of tests in range.[3] For each patient, test dates, INR results and INR range during the last six months before the date of recruitment were obtained from the patient's anticoagulation booklet and inputted into the template. This procedure was carried out for all 50

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[3]INRPRO. Rosendaal Linear Interpolation Method Template [Online]. 2017 [cited 2017 Jun 12]. Available from: URL: https://www.inrpro.com/rosendaal.asp.

patients taking warfarin to estimate the percentage of cases where the INR was not within TTR.

2.7 Calculating CHA$_2$DS$_2$-VASc score

The CHA$_2$DS$_2$-VASc score was calculated for each patient using the information collected in Section A, B and D of the data collection form. The points were added according to the conditions present in each patient to give a total CHA$_2$DS$_2$-VASc score (Table 2.6).

Table 2.6: CHA$_2$DS$_2$-VASc scoring system

	Condition	Points
C	Congestive heart failure (or Left ventricular systolic dysfunction)	1
H	Hypertension: Resting blood pressure >140/90 mmHg on at least two occasions or current antihypertensive treatment	1
A$_2$	Age ≥75 years	2
D	Diabetes Mellitus	1
S$_2$	Previous Stroke, TIA or thromboembolism	2
V	Vascular disease (Peripheral artery disease, MI, aortic plaque)	1
A	Age 65–74 years	1
Sc	Sex category (female sex)	1

Adopted from: Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijins HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: The euro heart survey on atrial fibrillation. Chest. 2010; 137(2): 263-72.

The calculated CHA$_2$DS$_2$-VASc score was used to determine the annual stroke risk, the higher the score the greater the annual stroke risk (Table 2.7).

Table 2.7: Annual stroke risk according to CHA$_2$DS$_2$-VASc score

CHA$_2$DS$_2$-VASc Score	Stroke Risk (%)	95% CI
0	1.9	1.2–3.0
1	2.8	2.0–3.8
2	4.0	3.1–5.1
3	5.9	4.6–7.3
4	8.5	6.3–11.1
5	12.5	8.2–17.5
6	18.2	10.5–27.4

Adopted from: Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S et al. Guidelines for the management of atrial fibrillation: The task force for the management of atrial fibrillation of the European Society of Cardiology (ESC). Eur Heart J. 2010; 31(19): 2369-429.

2.8 Identification of drug-drug interactions

The list of current medications documented in Section D of the data collection form, were used to identify potential DDIs between warfarin or rivaroxaban and other prescribed medications. The list of medications for each patient was inputted in the Micromedex® electronic database system[4] to identify potential DDIs with warfarin or rivaroxaban. The electronic database system classifies DDIs according to severity; minor, moderate or major. A minor DDI usually has limited clinical effects which may include an increase in severity and frequency of side-effects, but usually does not require any major change in therapy. A moderate DDI may exacerbate or worsen the patient's

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[4] Micromedex® 2.0. DRUG-REAX System [Online]. USA; 2017 [cited 2017 June 12]. Available from: URL: www.micromedexsolutions.com/micromedex2/4.14.0/WebHelp/Tools/Interactions/Drug_Interactions.htm

condition and usually requires a change in therapy. A major DDI can be potentially life-threatening and requires medical intervention to reduce or prevent serious side-effects (Soherwardi et al, 2012; Bhagavathula et al, 2014; Dixon et al, 2015). The procedure was repeated using the Medscape multi-drug interaction checker database[5] to confirm the DDIs identified with Micromedex®.

2.9 Cost Analysis

Table 2.8 describes the method of cost analysis for warfarin and rivaroxaban.

Table 2.8: Method of cost analysis

Process	Relation to Study
Define the Problem	No NOAC available on Maltese GFL
Identify alternative interventions	Comparison of rivaroxaban and warfarin
Identify and measure outcomes	Bleeding, DDIs, Adherence, Ischaemic outcomes, INR results out-of-range
Identify, measure and value costs	Direct medical costs – Drug, INR Monitoring and Physician costs

At the time of study two generic brands of warfarin were available from community pharmacies. The retail cost of each generic brand of warfarin was obtained from local distribution agents. Retail prices were checked for any amendments during the study

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[5] Medscape. Drug Interaction Checker [Online]. 2017 [cited 2017 Jun 12]. Available from: URL: www.reference.medscape.com/drug-interactionchecker

period up to March 2017. For the NHS cost, warfarin is available on the GFL and the March 2017 tender cost was obtained from CPSU.

The patient's current dose was used to calculate cost of warfarin treatment. Warfarin dose and cost is dependent on the INR result obtained. The cost of warfarin per Defined Daily Dose (DDD) was calculated to obtain a daily cost of warfarin. The cost for each patient over a six-month period was calculated.

For INR testing, the cost of laboratory-based testing was obtained from the Department of Pathology at MDH.[6] The cost of POC INR testing was obtained from a study carried out by Zammit et al (2010). The total cost of INR testing per patient was calculated by multiplying the number of tests in a 6-month period by the cost of either laboratory-based testing or POC testing.

At the time of the study, three NOACs (dabigatran, Pradaxa®; rivaroxaban, Xarelto®; apixaban, Eliquis®) were available on the retail market in Malta. Retail cost of each NOAC was obtained from local distribution agents. The retail prices were checked for any amendments during the study period up to March 2017.

No NOAC was available on the GFL at the time of the study and therefore no reference tender pricing was available. The wholesale prices of NOACs in the community setting were used as reference pricing, which represent the minimum cost saving the government could obtain, if purchased under tender. The wholesale prices of NOACs in

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[6] Bartolo V. Cost per INR test at 2012 prices. [e-mail] (Personal communication, February 2017).

a pharmacy is 20% less than the retail price. The cost for each patient over a six-month period was calculated.

The cost of a standard General Practitioner visit was obtained from nine GPs in six different localities representing the Northern Harbour, Southern Harbour, South Eastern and Western districts. The mean cost per GP visit was assumed to be the fee paid by each patient who visited the GP for an anticoagulation therapy-related visit. The cost was multiplied by the number of GP visits per patient over a six-month period.

2.10 Statistical analysis

Statistical analysis was performed using IBM SPSS® Statistics version 24. Equality of distribution between warfarin and rivaroxaban groups was analysed using the chi-square test for categorical variables (gender, age, level of education, living situation, smoking, alcohol, indication for anticoagulation, option to take a NOAC, prior knowledge about NOACs, bleeding and potential DDIs). For continuous variables (CHA$_2$DS$_2$-VASc score, duration of anticoagulation, chronic medications prescribed, adherence to anticoagulation and cost of anticoagulation treatment), normality of data was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Parametric tests, including the Mann-Whitney test, Spearman correlation co-efficient and Wilcoxon signed-rank test, and non-parametric, tests including the Friedman and Independent sample t-test were used to analyse continuous variables.

The chi-square test was used to assess the association between two categorical variables. One of the categorical variables indicates the anticoagulant prescribed

(warfarin/rivaroxaban) or adherence to anticoagulation, whilst the other variable was gender, age, level of education, living situation, smoking habits, alcohol consumption, indication for anticoagulation, option to take a NOAC, prior knowledge about NOACs, incidence of bleeding and DDI. The Null Hypothesis specifies that there is no association between two categorical variables and is accepted if the p-value exceeds the 0.05 level of significance. The Alternative Hypothesis specifies that there is a significant association between the two categorical variables and is accepted if the p-value is less than the 0.05 criterion.

The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess the normality of data for the CHA_2DS_2-VASc score, duration of anticoagulation, number of chronic medications, adherence to anticoagulation and mean cost of anticoagulants (Table 2.9). The null hypothesis specifies that the score distribution is normal and is accepted if the p-value exceeds the 0.05 level of significance. The alternative hypothesis specifies that the score distribution is skewed and is accepted if the p-value is less than the 0.05 criterion.

Table 2.9: Test of normality for continuous variables

	Kolmogorov-Smirnov			Shapiro-Wilk		
	Statistic	df	p-value	Statistic	Df	p-value
CHA_2DS_2-VASc Score	0.178	100	0.000	0.928	100	0.000
Duration of Anticoagulation	0.139	100	0.000	0.922	100	0.000
Number of Chronic Medications	0.178	100	0.000	0.920	100	0.000
Adherence to Anticoagulation	0.316	100	0.000	0.757	100	0.000
Mean Anticoagulation Cost	0.326	100	0.000	0.766	100	0.000

The Mann Whitney test was used to compare CHA_2DS_2-VASc score, duration of anticoagulation, chronic medications prescribed and mean adherence scores between two independent groups clustered by anticoagulant (warfarin/rivaroxaban), as the distribution between groups was not normal. The null hypothesis specifies that CHA_2DS_2-VASc score, duration of anticoagulation, chronic medications prescribed and mean adherence scores vary marginally between the two groups and is accepted if the p-value exceeds the 0.05 level of significance. The alternative hypothesis specifies that the CHA_2DS_2-VASc score, duration of anticoagulation, chronic medications prescribed and mean adherence scores differ significantly between the two groups and is accepted if the p-value is less than the 0.05 criterion.

The Friedman test was used to compare the mean proportion of patients not adherent to each question in the adherence questionnaire. The null hypothesis specifies that the mean proportion of adherent patients is similar between the questions and is accepted if the p-value exceeds the 0.05 level of significance. The alternative hypothesis specifies that the mean proportion of adherent patients varies significantly between the questions and is accepted if the p-value is less than the 0.05 criterion.

The Wilcoxon signed-rank test was used to compare the mean proportion of patients not adherent to each question in the adherence questionnaire. The null hypothesis specifies that the mean proportion of adherent patients is similar between the questions and is accepted if the p-value exceeds the 0.05 level of significance. The alternative hypothesis specifies that the mean proportion of adherent patients varies significantly between the questions and is accepted if the p-value is less than the 0.05 criterion.

The Spearman correlation co-efficient was used to measure the strength of the relationship between INR requests, number of times INR was not within range and adherence scores. The Spearman correlation co-efficient ranges from -1 to 1, where a positive co-efficient indicates a positive relationship and a negative co-efficient indicates a negative relationship. The null hypothesis specifies that there is no relationship between INR requests, number of times INR was not within range and adherence scores and is accepted if the p-value exceeds the 0.05 level of significance. The alternative hypothesis specifies that there is a significant relationship between INR requests, number of times INR was not within range and adherence scores and is accepted if the p-value is less than the 0.05 criterion.

The Independent sample t-test was used to compare mean cost between patients on warfarin and patients on rivaroxaban. The null hypothesis specifies that there is no association between mean cost of warfarin and rivaroxaban and is accepted if the p-value exceeds the 0.05 level of significance. The alternative hypothesis specifies that there is a significant association between mean cost of warfarin and rivaroxaban and is accepted if the p-value is less than the 0.05 criterion.

Chapter 3
Results

A total of 100 patients who met the study inclusion criteria were recruited (50 warfarin, 50 rivaroxaban). Patient demographics, social history, indication and duration of anticoagulation, option given and knowledge about NOACs, incidence and severity of bleeding, adherence to anticoagulation, INR testing, CHA_2DS_2-VASc score, chronic medications, DDIs, and cost comparison of anticoagulation treatment results are reported.

3.1 Patient demographics

Fifty-three patients were female and 47 were male. No significant difference in gender distribution between warfarin and rivaroxaban groups was observed (p>0.05) (Table 3.1).

Table 3.1: Gender distribution (N=100)

			Anticoagulant	
			Warfarin (n=50)	Rivaroxaban (n=50)
Gender	Male	Number of patients	23	24
		Percentage	46%	48%
	Female	Number of patients	27	26
		Percentage	54%	52%
$X^2(1) = 0.04$, p = 0.841				

Mean age was 63.9 ±12.91 (range 37-85) years for patients on warfarin and 65.2 ±13.01 (range 27-85) years for patients on rivaroxaban. No significant difference in age between warfarin and rivaroxaban groups was observed (p>0.05) (Table 3.2).

46

Table 3.2: Age distribution (N=100)

			Anticoagulant	
			Warfarin (n=50)	Rivaroxaban (n=50)
Age (years)	<60	Number of patients	16	14
		Percentage	32%	28%
	60-70	Number of patients	13	15
		Percentage	26%	30%
	71-80	Number of patients	18	17
		Percentage	36%	34%
	>80	Number of patients	3	4
		Percentage	6%	8%
$X^2(3) = 0.448$, $p = 0.930$				

Fifty-three patients in the total population had secondary level education. The difference in level of education between warfarin and rivaroxaban groups was statistically significant ($p<0.05$), with a higher level of education observed in the rivaroxaban group (Table 3.3).

Table 3.3: Level of education (N=100)

			Anticoagulant	
			Warfarin (n=50)	Rivaroxaban (n=50)
Level of Education	Primary	Number of patients	13	8
		Percentage	26%	16%
	Secondary	Number of patients	29	24
		Percentage	58%	48%
	Post-Secondary	Number of patients	3	14
		Percentage	6%	28%
	Tertiary	Number of patients	5	4
		Percentage	10%	8%
$X^2(3) = 8.891$, $p = 0.031$				

Eighty-three of the patients lived with their spouse/partner or other family members. No significant difference in living situation between warfarin and rivaroxaban groups was observed (p>0.05) (Table 3.4).

Table 3.4: Living situation (N=100)

			Anticoagulant	
			Warfarin (n=50)	Rivaroxaban (n=50)
Living Situation	Lives Alone	Number of patients	4	2
		Percentage	8%	4%
	Lives with Spouse/ Partner/Family	Number of patients	42	41
		Percentage	84%	82%
	Lives in a Long-Term Care facility	Number of patients	4	7
		Percentage	8%	14%
$X^2(2) = 1.497$, p = 0.473				

3.2 Social history

Seventy-five of the patients were non-smokers. No significant difference in smoking status between warfarin and rivaroxaban groups was observed (p>0.05) (Table 3.5).

Table 3.5: Current smoking (N=100)

			Anticoagulant	
			Warfarin (n=50)	Rivaroxaban (n=50)
Current Smoking	Yes	Number of Patients	12	13
		Percentage	24%	26%
	No	Number of Patients	38	37
		Percentage	76%	74%
$X^2(1) = 0.053$, p = 0.817				

Sixty-three of the patients never consumed alcohol. More patients in the rivaroxaban group (n=27) consumed alcohol and the difference between warfarin and rivaroxaban groups was statistically significant (p<0.05) (Table 3.6).

Table 3.6: Alcohol consumption (N=100)

			Anticoagulant	
			Warfarin (n=50)	Rivaroxaban (n=50)
Alcohol Consumption	Never	Number of Patients	36	27
		Percentage	72%	54%
	Socially	Number of Patients	8	18
		Percentage	16%	36%
	1-2 units a day	No. of Patients	2	5
		Percentage	4%	10%
	3-4 units a day	No. of Patients	4	0
		Percentage	8%	0%
$X^2(3) = 10.418$, p = 0.015				

3.3 Indication for anticoagulation

In the total study population, oral anticoagulation was predominantly indicated for AF
(n=59), followed by DVT (n=30) (Figure 3.1).
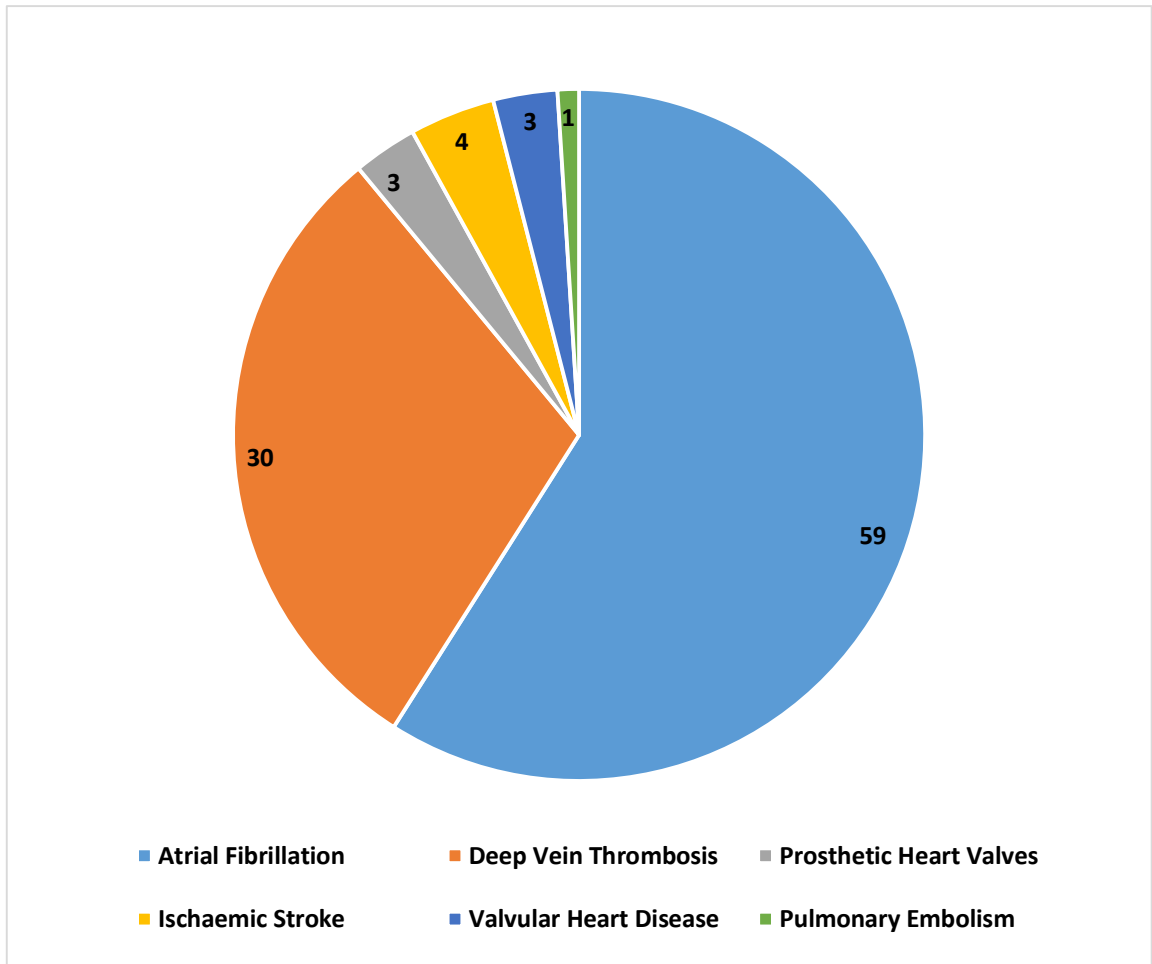
Figure 3.1: Indication for oral anticoagulation (N=100)

No significant difference in indication for anticoagulation between warfarin and rivaroxaban groups was observed (p>0.05) (Table 3.7).

Table 3.7: Indication for oral anticoagulation (N=100)

			Anticoagulant	
			Warfarin (n=50)	Rivaroxaban (n=50)
Indication	Atrial Fibrillation	Number of Patients	28	31
		Percentage	56%	62%
	Deep Vein Thrombosis	Number of Patients	13	17
		Percentage	26%	34%
	Ischaemic Stroke	Number of Patients	2	2
		Percentage	4%	4%
	Prosthetic Heart Valves	Number of Patients	3	0
		Percentage	6%	0%
	Pulmonary Embolism	Number of Patients	1	0
		Percentage	2%	0%
	Valvular Heart Disease	Number of Patients	3	0
		Percentage	6%	0%
$X^2(5) = 7.686$, p = 0.174				

3.4 Duration of anticoagulation

Seventy-five patients had been taking an anticoagulant for 12 months or less (Table 3.8).

Table 3.8: Duration of anticoagulation (N=100)

			Anticoagulant	
			Warfarin (n=50)	Rivaroxaban (n=50)
Duration (months)	1-6	Number of patients	13	13
		Percentage	26%	26%
	7-12	Number of patients	21	28
		Percentage	42%	56%
	13-18	Number of patients	9	6
		Percentage	18%	12%
	19-24	Number of patients	3	2
		Percentage	6%	4%
	25-30 months	Number of patients	2	1
		Percentage	4%	2%
	31-36 months	Number of patients	2	0
		Percentage	4%	0%
$X^2(5)$ = 4.133, p = 0.530				

The mean duration of anticoagulation was 11 ±6.89 (range 1-33) months for patients on warfarin and 9 ±5.04 (range 1-24) months for patients on rivaroxaban. No significant difference in duration of anticoagulation between warfarin and rivaroxaban groups was observed (p>0.05) (Table 3.9).

Table 3.9: Mean duration of anticoagulation (N=100)

	Anticoagulant	Mean	SD	p-value (Mann-Whitney)
Mean Duration of Anticoagulation	Warfarin	11.02	6.888	0.197
	Rivaroxaban	9.10	5.044	

3.5 Novel oral anticoagulants as an alternative treatment option

Out of the 100 patients, 57 were given the option by their consultant to start a NOAC when oral anticoagulantion therapy was initially prescribed. Thirty-nine of these patients followed the consultants' advice and opted for NOAC therapy. The difference was statistically significant (p<0.001) (Table 3.10).

Table 3.10: Advice on novel oral anticoagulants as a treatment option (N=100)

			Anticoagulant	
			Warfarin (n=50)	Rivaroxaban (n=50)
Given NOAC option at time of initial prescription of anticoagulation therapy	Yes	Number of Patients	18	39
		Percentage	36%	78%
	No	Number of Patients	32	11
		Percentage	64%	22%
$X^2(1)$ = 17.993, p = <0.001				

3.6 Incidence and severity of bleeding since anticoagulant initiation

Sixty-six patients did not experience any bleeding. Patients on warfarin experienced more BARC Type 1 and Type 2 bleeding; bruising (n=18), gingival bleeds (n=2), epistaxis (n=3) and rectal bleeds (n=1), compared to patients on rivaroxaban; bruising (n=6), gingival bleeds (n=2) and epistaxis (n=2). Difference in bleeding between warfarin and rivaroxaban groups was statistically significant (p<0.05) (Figure 3.2).
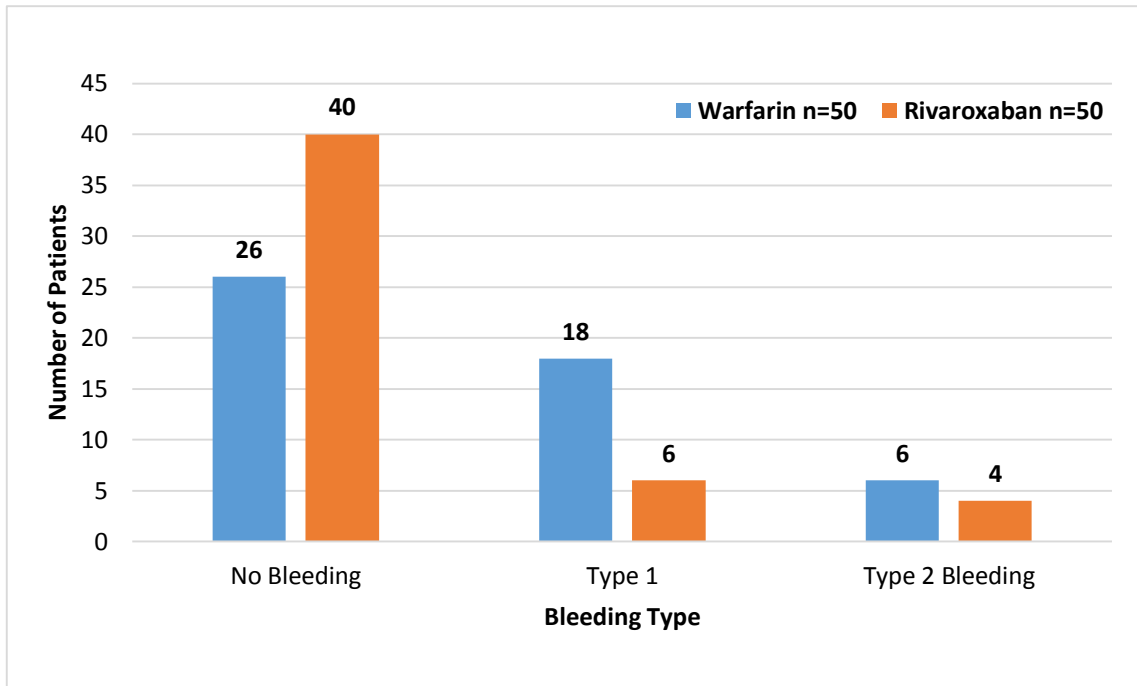
X^2(2) = 9.370, p=0.009

Figure 3.2: Incidence and severity of bleeding (N=100)

3.7 Adherence to anticoagulation

The mean adherence score for the 9 questions in the adherence questionnaire was 40.82 (SD 3.916) out of 45 for patients on warfarin (range 30-45) and 44.02 (SD 1.407) out of 45 for patients on rivaroxaban (range 39-45). Patients on rivaroxaban obtained a significantly higher mean adherence score compared to patients on warfarin (Mann-Whitney; p<0.001).

Adherence for both warfarin and rivaroxaban groups was highest for questions 4, 7 and 9 in the adherence questionnaire. The lowest adherence scores for warfarin were obtained in questions 1, 5 and 6 and in questions 2, 5 and 6 for rivaroxaban.

When analysing each question separately, patients in the rivaroxaban group scored higher for all 9 questions compared to patients on warfarin. The difference in mean

adherence score between patients on warfarin and rivaroxaban was significant (p<0.05)

in 6 out of the 9 questions (Table 3.11).

Table 3.11: Mean adherence score for each statement in adherence questionnaire (N=100)

Question	Anticoagulant	Mean (Range)	SD	p-value (Wilcoxon Signed-Rank Test)
1. Do you take your prescribed warfarin/rivaroxaban?	Warfarin (n=50)	4.30 (2-5)	1.035	**0.004***
	Rivaroxaban (n=50)	4.86 (4-5)	0.351	
2. Do you take warfarin/rivaroxaban at their prescribed times?	Warfarin (n=50)	4.50 (2-5)	0.931	0.090
	Rivaroxaban (n=50)	4.82 (3-5)	0.482	
3. If you travel abroad, do you take along warfarin/rivaroxaban?	Warfarin (n=50)	4.40 (2-5)	0.782	**0.000***
	Rivaroxaban (n=50)	4.90 (4-5)	0.303	
4. Were there any occasions were you stopped taking warfarin/rivaroxaban out of your own free will?	Warfarin (n=50)	4.86 (4-5)	0.351	0.082
	Rivaroxaban (n=50)	4.96 (4-5)	0.198	
5. Did you ever miss a dose?	Warfarin (n=50)	4.16 (2-5)	1.037	**0.001***
	Rivaroxaban (n=50)	4.80 (3-5)	0.452	
6. Did you miss/stop treatment because you forgot?	Warfarin (n=50)	4.30 (2-5)	1.035	**0.008***
	Rivaroxaban (n=50)	4.82 (3-5)	0.438	
7. Did you miss/stop treatment, because you experienced adverse effects?	Warfarin (n=50)	4.88 (3-5)	0.385	0.092
	Rivaroxaban (n=50)	4.98 (4-5)	0.141	
8. Did you miss/stop warfarin/rivaroxaban, because you have too many medicines and you got confused on how they should be administered?	Warfarin (n=50)	4.60 (3-5)	0.756	**0.040***
	Rivaroxaban (n=50)	4.90 (4-5)	0.303	
9. Did you miss/stop treatment, because you felt good and decided that you did not need the medicine?	Warfarin (n=50)	4.82 (3-5)	0.438	**0.015***
	Rivaroxaban (n=50)	4.98 (4-5)	0.141	

*p<0.05: statistically significant

3.8 INR monitoring

Forty-four patients taking warfarin monitor the INR by means of the laboratory-based method at the ACC, while the other 6 patients test their INR by means of POC testing at a government health centre. Twenty-three patients complained about the inconvenience of having to routinely monitor the INR, while the other twenty-seven patients stated that they had accepted and understood the importance of regular INR monitoring.

The total number of INR tests in a 6-month period for the 50 patients on warfarin was 768, corresponding to 128 INR tests per month. The mean number of INR tests per patient per month was 2.56 ±1.58 (range 1-7 tests). Of the 128 INR tests, 37% (n=47) were not within TTR (Figure 3.3).
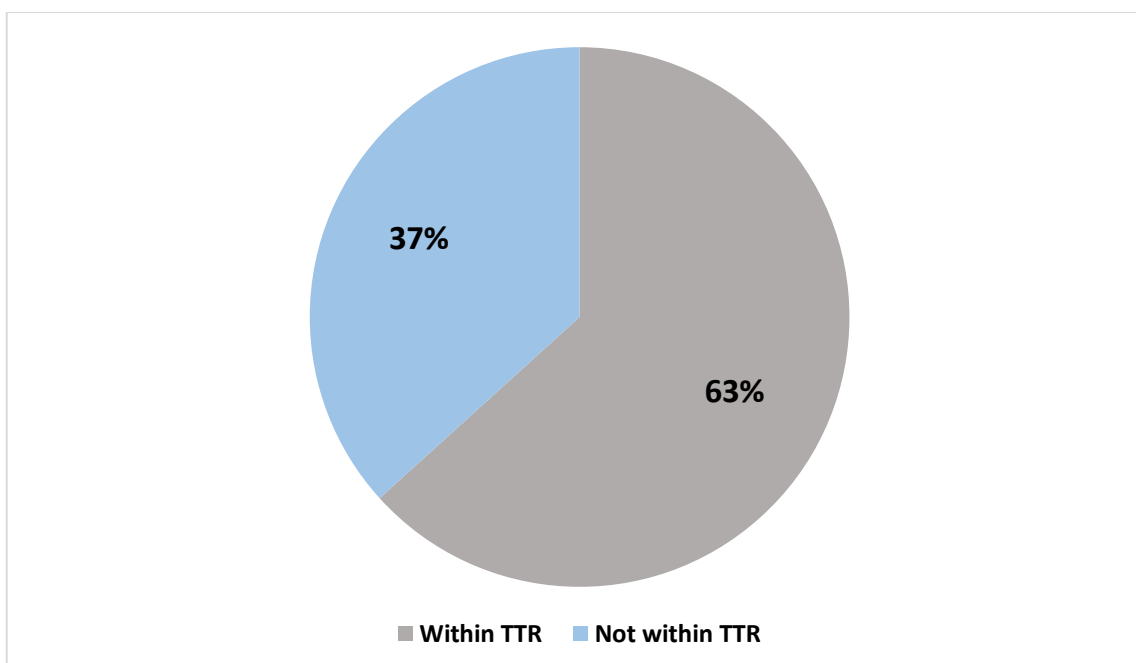
Figure 3.3: Time in therapeutic range (n=128)

The majority of patients on warfarin with fewer number of chronic medications had a more stable INR with less time out-of-range compared to patients with a greater number of chronic medications. This difference was statistically significant (p<0.001) (Table 3.12).

Table 3.12: Cross tabulation: INR out-of-range versus number of chronic medications

			Number of Chronic Medications			
			1-3	4-6	7-9	10-12
Number of times INR Out-Of-Range	0-4	Number of patients	6	15	1	1
		Percentage	26.1%	65.2%	4.3%	4.3%
	5-8	Number of patients	10	5	0	2
		Percentage	58.5%	29.4%	0%	11.8%
	9-12	Number of patients	1	4	0	1
		Percentage	16.7%	66.7%	0%	16.7%
	13-16	Number of patients	0	0	1	0
		Percentage	0%	0%	100%	0%
	17-20	Number of patients	0	0	0	1
		Percentage	0%	0%	0%	100%
	21-24	Number of patients	0	1	0	0
		Percentage	0%	100%	0%	0%
	25-28	Number of patients	1	0	0	0
		Percentage	100%	0%	0%	0%
$X^2(18) = 44.31$, p <0.001						

3.9 CHA$_2$DS$_2$-VASc score and stroke risk

The mean CHA$_2$DS$_2$-VASc score was 2.02 ±1.15 (range 0-5) for patients on warfarin and 2.20 ±1.18 (range 0-4) for patients on rivaroxaban. No significant difference in CHA$_2$DS$_2$-VASc score between warfarin and rivaroxaban groups was observed (p>0.05) (Table 3.13).

Table 3.13: Mean CHA$_2$DS$_2$-VASc score (N=100)

	Anticoagulant	Mean	SD	p-value (Mann-Whitney)
Mean CHA$_2$DS$_2$-VASc Score	Warfarin (n=50)	2.02	1.152	0.349
	Rivaroxaban (n=50)	2.20	1.178	

The mean annual stroke risk was 4.47 ±2.55% (range 1.9-12.5%) for patients on warfarin and 4.75 ±2.40% (range 1.9-8.5%) for patients on rivaroxaban. No significant difference in mean annual stroke risk between warfarin and rivaroxaban groups was observed (p>0.05) (Table 3.14).

Table 3.14: Mean annual stroke risk (N=100)

	Anticoagulant	Mean	SD	p-value (Mann-Whitney)
Mean Annual Stroke Risk	Warfarin (n=50)	4.47	2.236	0.714
	Rivaroxaban (n=50)	4.75	1.949	

3.10 Polypharmacy

The total number of chronic medications for all the 100 patients, including anticoagulants, was 477. The mean number of medications per patient was 4.77 ±2.57 (range 1-12). Forty-seven patients were taking between 5 and 8 medications (Table 3.15).

Table 3.15: Polypharmacy (N=100)

Number of chronic medications	Number of patients
1-4	45
5-8	47
9-12	8

The mean number of chronic medications was 4.62 ±2.63 (range 1-11) for patients on warfarin and 4.92 ±2.28 (range 1-12) for patients on rivaroxaban. No significant difference in mean number of chronic medications between patients on warfarin and rivaroxaban was observed (p>0.05) (Table 3.16).

Table 3.16: Mean number of chronic medications (N=100)

	Anticoagulant	Mean	SD	p-value (Mann-Whitney)
Mean Number of Chronic Medications	Warfarin (n=50)	4.62	2.633	0.369
	Rivaroxaban (n=50)	4.92	2.284	

Statins (n=62, 13%) and ACE inhibitors (n=53, 11%) were the most commonly prescribed chronic medications when excluding warfarin and rivaroxaban (Figure 3.4). 'Other' chronic medications not included in Figure 3.4 were anticonvulsants (n=3), non-opioid analgesics (n=3), antipsychotics (n=2), disease modifying antirheumatic drugs (n=1), drugs for gout (n=1), flavonoids (n=1), vitamins and supplements (n=1).

Simvastatin (n=54), perindopril (n=47) and bumetanide (n=26) were the top three prescribed chronic medications according to generic name.
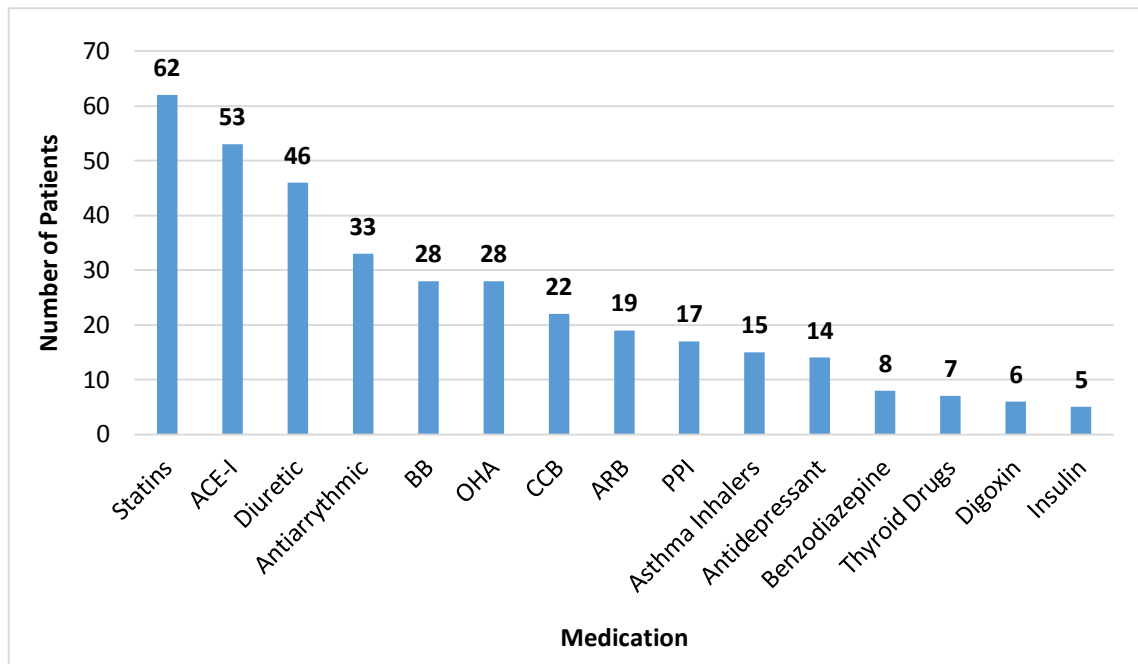
ACE-I: Angiotensin converting enzyme inhibitor; **ARB:** Angiotensin-II receptor blocker; **BB:** Beta-blocker; **CCB:** Calcium channel blocker **OHA:** Oral hypoglycaemic agent; **PPI:** Proton pump inhibitor

Figure 3.4: Chronic medications (N=363)

3.11 Drug-drug interactions

For the 50 patients on warfarin, 91 potential DDIs were identified, with a mean of 1.82 ±1.03 (range 0-4) DDIs per patient. For rivaroxaban, 19 potential drug DDIs were identified with a mean of 0.38 ±0.52 (range 0-2) DDIs per patient. The number of potential DDIs in patients on warfarin was significantly higher than patients on rivaroxaban (p<0.001) (Table 3.16). Simvastatin (n=24), amiodarone (n=12) and omeprazole (n=11) were the drugs implicated in highest number of DDIs with warfarin. Amiodarone (n=7), paroxetine (n=3) and verapamil (n=3) were the drugs implicated in the highest number of DDIs with rivaroxaban.

Table 3.17: Potential drug-drug interactions (N=100)

			Anticoagulant	
			Warfarin (n=50)	Rivaroxaban (n=50)
Number of potential DDIs	0	Number of Patients	3	32
		Percentage	6%	64%
	1	Number of Patients	21	17
		Percentage	42%	34%
	2	Number of Patients	10	1
		Percentage	20%	2%
	3	Number of Patients	14	0
		Percentage	28%	0%
	4	Number of Patients	2	0
		Percentage	4%	0%
$X^2(4) = 47.81$, p <0.001				

A total of 52 potential 'minor' DDIs with warfarin were identified, with a mean of 1.04 ±0.82 (range 0-3) DDIs per patient. Three 'minor' DDIs with rivaroxaban were identified, with a mean of 0.06 ±0.24 (range 0-1) DDIs per patient. The number of potential minor DDIs in patients taking warfarin was significantly higher than patients on rivaroxaban (p<0.001) (Table 3.18).

Table 3.18: Minor drug-drug interactions (N=100)

			Anticoagulant	
			Warfarin (n=50)	Rivaroxaban (n=50)
Number of potential minor DDIs	0	Number of Patients	13	47
		Percentage	26%	94%
	1	Number of Patients	25	3
		Percentage	50%	6%
	2	Number of Patients	9	0
		Percentage	18%	0%
	3	Number of Patients	3	0
		Percentage	6%	0%
$X^2(3) = 48.55$, p <0.001				

A total of 27 potential 'moderate' DDIs with warfarin were identified, with a mean of 0.54 ±0.61 (range 0-2) DDIs per patient. Fourteen 'moderate' DDIs with rivaroxaban were identified, with a mean of 0.28 ±0.45 (range 0-1) DDIs per patient. The number of potential 'moderate' DDIs in patients on warfarin was significantly higher than patients on rivaroxaban (p<0.05) (Table 3.19).

Table 3.19: Moderate drug-drug interactions (N=100)

			Anticoagulant	
			Warfarin (n=50)	Rivaroxaban (n=50)
Number of potential moderate DDIs	0	Number of Patients	26	36
		Percentage	52%	72%
	1	Number of Patients	21	14
		Percentage	42%	28%
	2	Number of Patients	3	0
		Percentage	6%	0%
$X^2(2) = 6.01$, p = 0.049				

A total of 12 potential 'major' DDIs with warfarin were identified, with a mean of 0.24 ±0.43 (range 0-1) DDIs per patient. Two 'major' DDIs with rivaroxaban were identified, with a mean of 0.04 ±0.19 (range 0-1) DDIs per patient. The number of potential 'major' DDIs in patients on warfarin was significantly higher than patients on rivaroxaban (p<0.05) (Table 3.20).

Table 3.20: Major drug-drug interactions (N=100)

			Anticoagulant	
			Warfarin (n=50)	Rivaroxaban (n=50)
Number of potential major DDIs	0	Number of Patients	38	48
		Percentage	76%	96%
	1	Number of Patients	12	2
		Percentage	24%	4%
$X^2(1) = 8.31$, p = 0.004				

Patients on warfarin had at a higher risk of potential 'minor', 'moderate' and 'major' DDIs compared to patients on rivaroxaban. The difference in potential DDIs between patients on warfarin and rivaroxaban was statistically significant (p<0.001) (Figure 3.5).
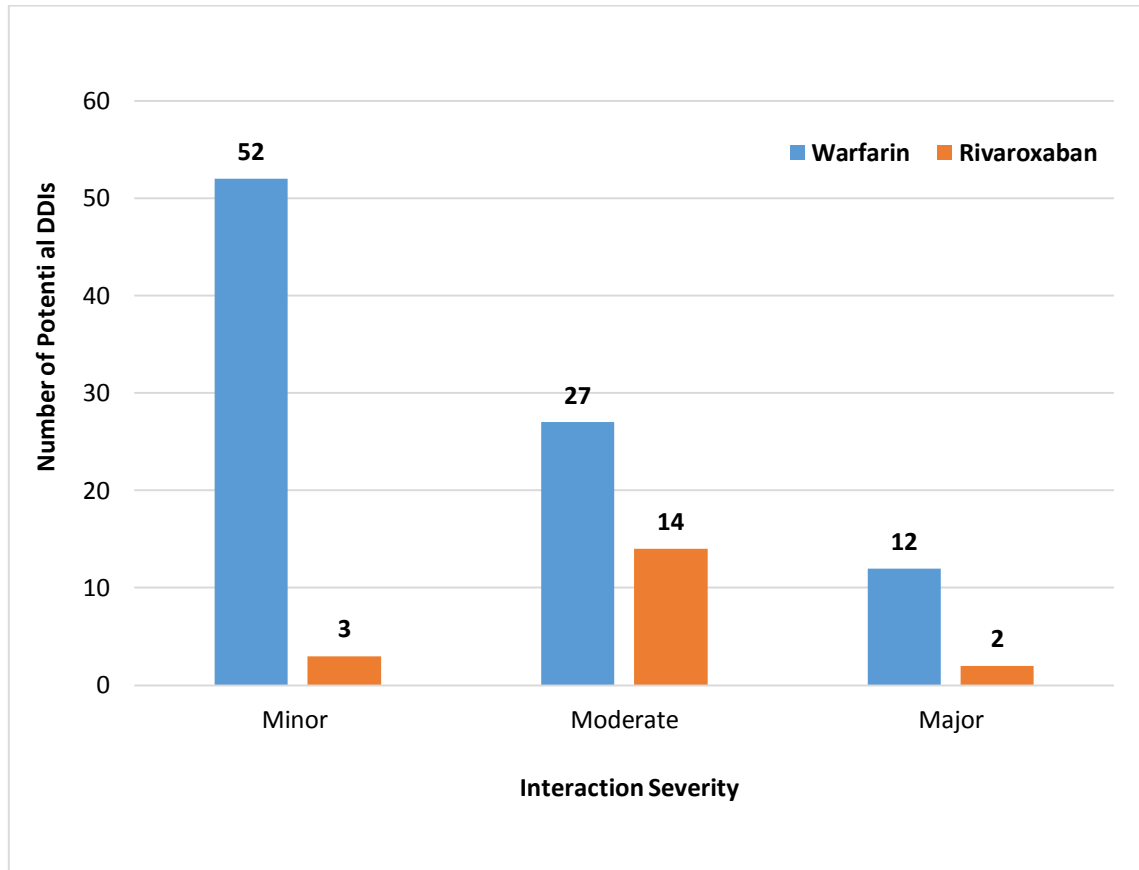
$X^2(4) = 47.81$, p<0.001

Figure 3.5: Comparison of potential DDIs (N=111)

3.12 Cost analysis

The NHS cost and retail cost of warfarin are summarised in Table 3.21.

Table 3.21: Comparison of NHS and retail cost of warfarin

Dose/Number of tablets	Government Health Service Cost (€)	Retail Cost (€)
1mg/28 tablets	0.310	1.700
1mg/tablet	0.011	0.061
3mg/28 tablets	0.390	2.950
3mg/tablet	0.014	0.105
5mg/28 tablets	0.420	3.680
5mg/tablet	0.015	0.131

The cost of warfarin per defined daily dose (DDD) was used to obtain the daily cost of warfarin (Table 3.22).

Table 3.22: Cost of warfarin per defined daily dose (DDD)

Dose (mg)	Government Health Service Cost per dose (€)	Retail Cost per dose (€)
0.5	€0.006	€0.037
1.0	€0.011	€0.061
1.5	€0.007	€0.053
2.0	€0.022	€0.121
2.5	€0.008	€0.064
3.0	€0.014	€0.105
3.5	€0.020	€0.159
4.0	€0.025	€0.189
4.5	€0.021	€0.158
5.0	€0.015	€0.129
5.5	€0.021	€0.159
6.0	€0.026	€0.189
6.5	€0.022	€0.181
7.0	€0.037	€0.25
7.5	€0.023	€0.193
8.0	€0.029	€0.234
8.5	€0.035	€0.254
9.0	€0.040	€0.295
9.5	€0.046	€0.314
10.0	€0.030	€0.257

The government health service cost of warfarin for the 50 patients recruited was €23.87 per month and the retail cost was €210.73 per month. The retail cost of NOACs available on the Maltese market were compared in Table 3.23. The government cost of rivaroxaban per patient per month was €81.25.

Table 3.23: Comparison of retail cost of novel oral anticoagulants

Pradaxa® (Dabigatran)		Xarelto® (Rivaroxaban)		Eliquis® (Apixaban)	
Dose/Number of tablets	Retail Cost (€)	Dose/Number of tablets	Retail Cost (€)	Dose/Number of tablets	Retail Cost (€)
110mg/10 tablets	15.87	10mg/10 tablets	38.40	2.5mg/60 tablets	105.00
110mg/tablet	1.59	10mg/tablet	3.84	2.5mg/tablet	1.75
150mg/60 tablets	93.08	15mg/42 tablets	158.60	5mg/56 tablets	98.00
150mg/tablet	1.55	15mg/tablet	3.78	5mg/tablet	1.75
		20mg/28 tablets	90.00		
		20mg/tablet	3.21		

The cost of a laboratory-based INR testing (2012) was €7.88 per test and the cost of POC testing (2010) was €4.22 per test (Table 3.24).

Table 3.24: Cost summary of INR testing

	Laboratory-based INR testing	POC testing
Number of patients	44	6
Number of tests/ 6 months	691	77
Mean tests/patient/month	2.6	2.1
Total Cost/6 Months	€5,445.08	€324.92
Mean total cost/patient/month	**€20.63**	**€9.03**

The mean cost per GP visit was €10 ±3.06 (range €5-€15) and was assumed to be the fee paid by each patient who visited the GP for an anticoagulation therapy-related visit. The total cost of GP visits was €230.00 for patients on warfarin and €80.00 for patients on rivaroxaban (Table 3.25).

Table 3.25: Cost summary of GP visits

	Warfarin (n=50)	Rivaroxaban (n=50)
Number of patients requiring GP visits	7	2
Total number of GP visits in 6 months	23	8
Total Cost	€230.00	€80.00

No bleeding episodes and ischaemic outcomes requiring hospital admission were reported by the patients recruited in this study, hence related costs were not calculated.

The mean cost per patient per month from a government health service perspective was €20.48 ±12.6 (range €6.91 - €55.53) for patients on warfarin and €81.52 ±0.47 (range €81.25 - €84.58) for patients on rivaroxaban. The difference in the total cost between warfarin and rivaroxaban groups was statistically significant ($p<0.001$) (Table 3.26).

Table 3.26: Government health service cost of warfarin and rivaroxaban (N=100)

	Warfarin (n=50)	Rivaroxaban (n=50)
Drug Cost	€143.23	€24,375.00
Cost of INR Testing	€5770.02	N/A
Cost of GP Vists	€230.00	€80.00
Total Cost/6 Months	€6,143.25	€24,455.00
Mean total cost/patient/month	€20.48	€81.52
$t(98) = -31.72$, $p < 0.001$		

The mean cost per patient per month from a retail cost perspective was €24.21 ±13.00 (range €11.07 - €59.68) for patients on warfarin and €97.77 ±0.47 (range €97.50 - €100.83) for patients on rivaroxaban. The retail cost difference between warfarin and rivaroxaban groups was statistically significant ($p<0.001$) (Table 3.27).

Table 3.27: Retail cost of warfarin and rivaroxaban (N=100)

	Warfarin (n=50)	Rivaroxaban (n=50)
Drug Cost	€1264.40	€29250.00
Cost of INR Testing	€5770.02	N/A
Cost of GP Vists	€230.00	€80.00
Total Cost/6 Months	€7,264.42	€29,330.00
Mean total cost/patient/month	**€24.21**	**€97.77**
t(98) = -37.63, p < 0.001		

3.13 Factors affecting adherence

When correlating adherence rates for warfarin with gender, living situation, social history, indication and duration for anticoagulation, bleeding outcomes, INR monitoring, CHA_2DS_2-VASc score, polypharmacy, DDI and cost no statistically significant association was obtained (p>0.05) (Table 3.27).

When correlating adherence rates for rivaroxaban with gender, age, level of education, living situation, social history, indication and duration for anticoagulation, bleeding outcomes, INR monitoring, CHA_2DS_2-VASc score, polypharmacy, DDI and cost no statistically significant association was obtained (p>0.05) (Table 3.28)

Table 3.28: Correlation between warfarin/rivaroxaban and factors affecting adherence

	Warfarin (n=50) p-value	Rivaroxaban (n=50) p-value
Gender	0.774	0.706
Age	**0.028***	0.774
Level of Education	**0.043***	0.774
Living Situation	0.596	0.543
CHA$_2$DS$_2$-VASc Score	0.795	0.963
Smoking	0.885	0.747
Alcohol	0.831	0.439
INR Monitoring	0.744	N/A
Indication for Anticoagulation	0.113	0.057
Duration of Anticoagulation	0.295	0.922
Bleeding	0.585	0.708
Polypharmacy	0.806	0.875
Drug-drug Interactions	0.396	0.072
Cost	0.356	0.325

Warfarin patients in the ≥71 years age category had lower adherence compared to younger patients. This difference was statistically significant (p<0.05) (Table 3.29).

Table 3.29: Cross tabulation: Warfarin adherence score versus age (n=50)

			Warfarin Adherence Score			
			30-33	34-37	38-41	42-45
Age (years)	<60	Number of patients	0	1	2	13
		Percentage	0%	6.3%	12.5%	81.3%
	60-70	Number of patients	1	3	1	8
		Percentage	7.7%	23.1%	7.7%	61.5%
	71-80	Number of patients	0	6	7	5
		Percentage	0%	33.3%	38.9%	27.8%
	>80	Number of patients	0	2	1	0
		Percentage	0%	66.7%	33.3%	0%
X^2(9) = 18.706, p = 0.028						

Eleven patients on warfarin with primary level education had lower adherence compared to patients with higher education levels. This difference was statistically significant (p<0.05) (Table 3.30).

Table 3.30: Cross tabulation: Warfarin adherence score versus level of education (n=50)

			Warfarin Adherence Score			
			30-33	34-37	38-41	42-45
Level of Education	Primary	Number of patients	1	7	3	2
		Percentage	7.7%	53.8%	23.1%	15.4%
	Secondary	Number of patients	0	5	7	17
		Percentage	0%	17.2%	24.1%	58.6%
	Post-Secondary	Number of patients	0	0	1	2
		Percentage	0%	0%	33.3%	66.7%
	Tertiary	Number of patients	0	0	0	5
		Percentage	0%	0%	0%	100%
$X^2(9) = 17.421$, p = 0.043						

The number of INR tests and number of times the INR was not within range were positively correlated with adherence score. This difference was statistically significant (p<0.05) (Table 3.31).

Table 3.31: Relationship between adherence score, INR tests and number of times INR out-of-range

		Adherence Score	INR Tests	Number of times INR out-of-range
Adherence Score	Spearman Correlation Coefficient	1.000	-0.263	-0.476
	P-value	N/A	0.045	0.000
INR Tests	Spearman Correlation Coefficient	-0.263	1.000	0.414
	P-value	0.045	N/A	0.003
Number of times INR out-of-range	Spearman Correlation Coefficient	-0.476	0.414	1.000
	P-value	0.000	0.003	N/A

Total adherence score was directly correlated to the frequency of INR tests. The lower the adherence score, the higher the number of INR tests carried out. This correlation was statistically significant (p<0.05) (Figure 3.6).

Figure 3.6: Relationship between adherence score and INR tests (n=50)
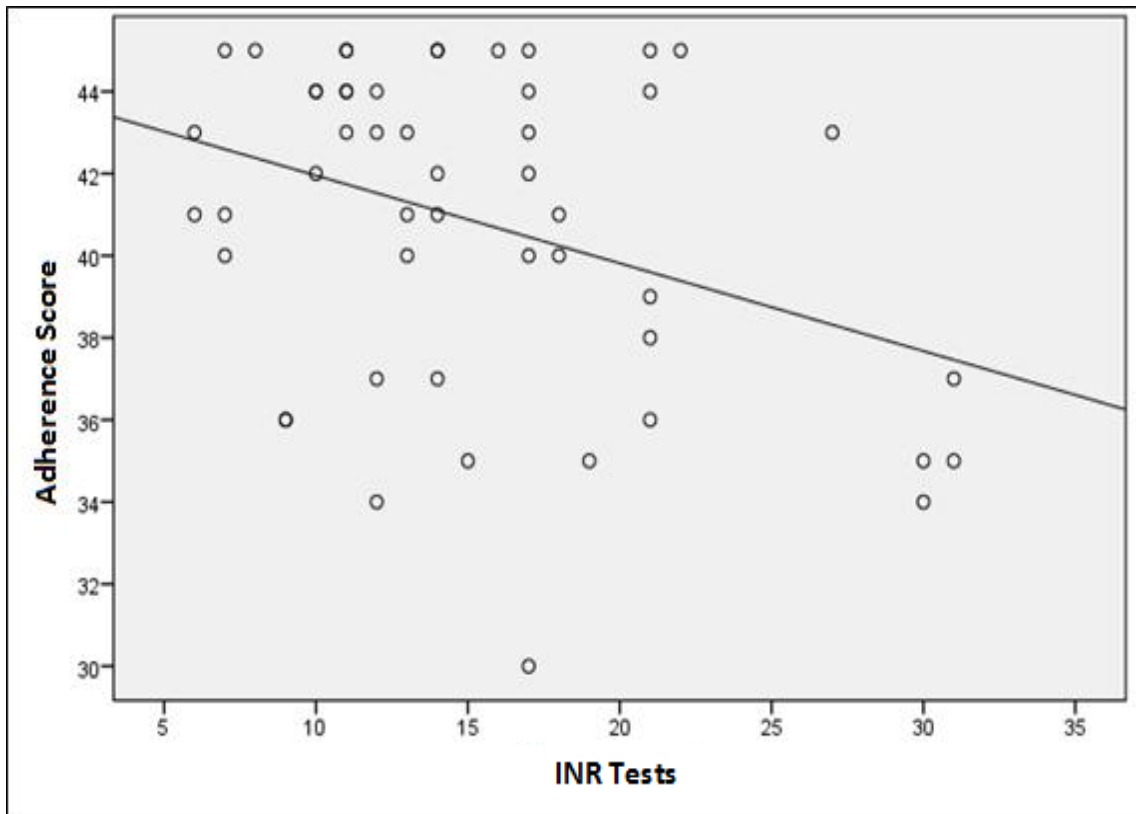
The total adherence score was directly correlated to the number of out-of-range INR tests. The lower the adherence score, the higher the number of out-of-range INR tests. This correlation was statistically significant (p<0.05) (Figure 3.7).

Figure 3.7: Relationship between adherence score and INR out-of-range (n=50)
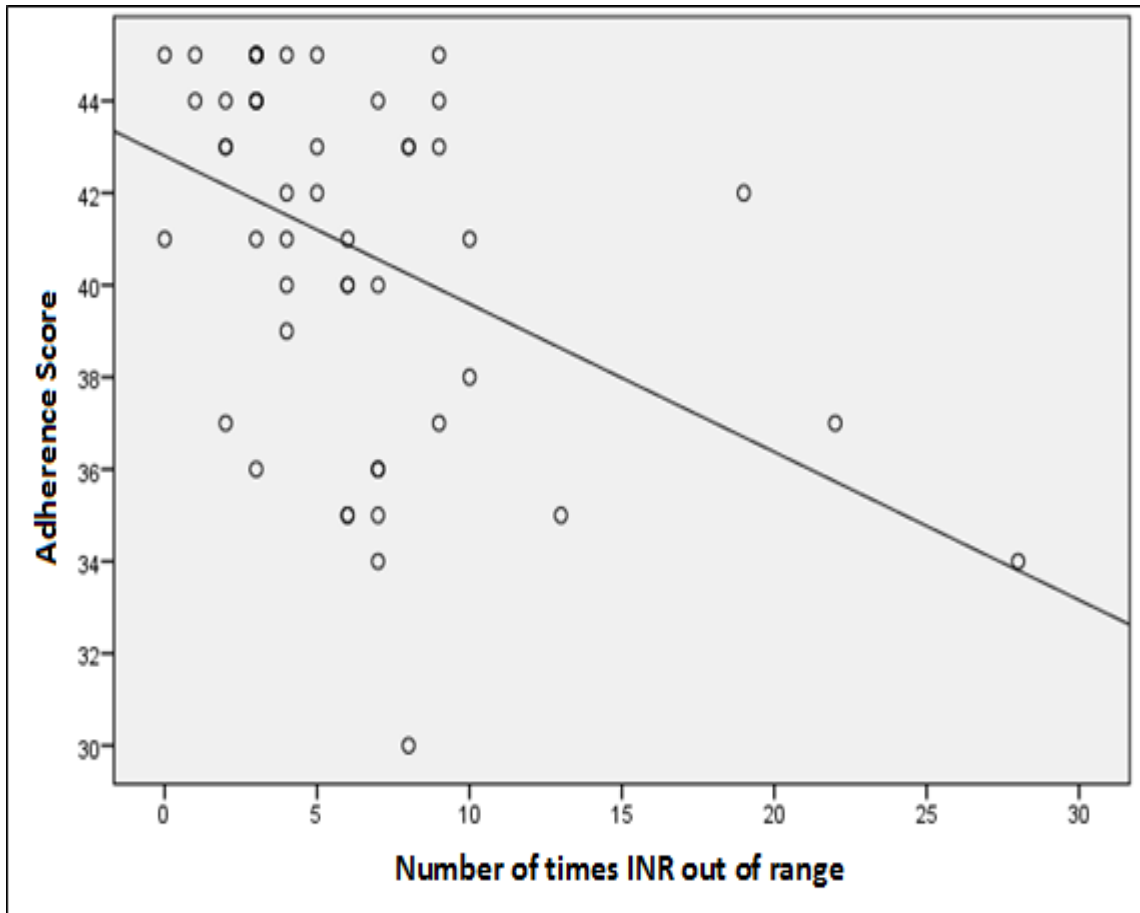
Chapter 4
Discussion

4.1 Interpretation and comparison of findings to similar studies

The incidence and severity of bleeding, treatment adherence, potential DDIs and cost differences between of warfarin and rivaroxaban were compared and INR control in patients on warfarin was assessed. During the preliminary study, it was observed that rivaroxaban is the predominantly prescribed NOAC in Malta. For this reason, dabigatran and apixaban were excluded and a direct comparison between warfarin and rivaroxaban was undertaken.

Score matching has been used in various clinical studies to carry out direct comparisons between rivaroxaban and warfarin (Maura et al, 2015; Coleman et al, 2016a; Lip et al, 2016a; Larsen et al, 2017). In the present study, patients in the warfarin and rivaroxaban groups were comparable ($p>0.05$) for age, gender, living situation, smoking status, indication and duration of anticoagulation use and CHA_2DS_2-VASc score, which allowed a better direct comparison between groups. Patient groups differ significantly ($p<0.05$) for level of education, alcohol consumption, incidence and severity of bleeding, treatment adherence, potential DDIs and cost.

Oral anticoagulation is most commonly prescribed in AF and VTE (Barnes et al, 2015; Whitworth et al, 2017), which was reflected in the present study. The rates of AF in Europe are low (0.12-0.16%) in patients younger than 50 years, higher (3.7-4.2%) in the 60-70 years age group and highest (10-17%) over 80 years of age (Berisso et al, 2014; Schnabel et al, 2015). Patients aged 40 years or older have approximately a 25% lifetime risk of developing AF (Marinigh et al, 2010). Males are more likely to develop AF when compared to females, however since women outnumber men in older age groups, the

total number of men and women with AF is reported to be similar (Marinigh et al, 2010). Similar results were observed in the present study where AF was more predominant in the 60 to 70 years age group and incidence was similar in both males and females. Incidence of VTE also increases markedly with age, with a sharp increase over the age of 50 years. Incidence rates are higher for women of childbearing age (16-45 years) and higher for men older than 45 years (Heit et al, 2016). Similar results were obtained in the present study showing that DVT was more predominant in the 50 to 60 years age group. The present study had a high number of women with childbearing age which resulted in women having a higher incidence of DVT compared to men.

Successful therapeutic use of an oral anticoagulant involves achieving a balance between decreasing the risk of thrombus formation and minimising the risk of bleeding complications (Qiang and Anthony, 2011; Streiff et al, 2016). Bleeding is reported to be a reason for discontinuation of and non-adherence to anticoagulation therapy (Ayabe et al, 2016; Yao et al, 2016). In the present study, patients reported BARC Type 1 and 2 bleeding which did not require hospitalisation and none of the patients experienced any major bleeding, including GI bleeding, intracranial haemorrhage (ICH) or extracranial haemorrhage (ECH). The results observed are conflicting with the ROCKET-AF trial, where incidence of major bleeding was 3.45% per year for warfarin and 3.60% per year for rivaroxaban (Patel et al, 2011). Other studies also show conflicting results to those reported in this study (Lip et al, 2016; Yao et al, 2016; Halvorsen et al, 2017). This difference may be attributed to the small sample size of 100 patients compared to the ROCKET-AF trial (N=14,264) and other studies which included a much larger sample size. Moreover, the patients in the present study had a mean anticoagulation duration of 11

months for warfarin and 9 months for rivaroxaban, with 75% of the total cohort being on anticoagulation therapy for one year or less. No patient follow-up was carried out. In contrast, the ROCKET-AF trial and other trials followed up patients for a number of years.

Studies have shown that bleeding rates in patients taking a NOAC are usually similar or lower compared to patients taking warfarin (Larsen et al, 2016; Lip et al, 2016b; Yao et al, 2016; Halvorsen et al, 2017). ICH and ECH are major bleeding complications associated with anticoagulation treatment. Dabigatran, rivaroxaban and apixaban have a lower risk of ICH and ECH compared to warfarin (Chatterjee et al, 2013; Hankey 2014; Ruff et al, 2016; Larsen et al, 2016; Yao et al, 2016). Other studies report that dabigatran and apixaban are associated with lower risks of ICH and ECH compared to warfarin and rivaroxaban (Staerk et al, 2016; Halvorsen et al, 2017). This is consistent with the findings of the RE-LY, ROCKET-AF and ARISTOTLE trials (Connolly et al, 2009; Patel et al, 2011; Granger et al, 2011).

Patients receiving anticoagulants are at a higher risk of GI complications, including gastrointestinal and abdominal pain, dyspepsia, nausea, constipation, diarrhoea and vomiting, and bleeding (Gutermann et al, 2015; Cheung and Leung et al, 2017). Conflicting results exist between studies comparing GI bleeding with warfarin and NOACs. In a study carried out by Yao et al (2016), compared to warfarin, apixaban had a significantly lower risk of GI bleeding, dabigatran showed no significant difference in GI bleeding and rivaroxaban was associated with an increased risk of GI bleeding. In two retrospective cohort studies, GI bleeding rates were similar for patients on dabigatran or rivaroxaban compared to warfarin (Abraham et al, 2015; Chang et al, 2015). Simlarily to the RE-LY, ROCKET-AF and ARISTOTLE trials (Connolly et al, 2009; Patel et al, 2011;

Granger et al, 2011), other studies have reported that dabigatran and rivaroxaban are associated with a higher risk of GI bleeding compared to warfarin, whilst apixaban is associated with a lower risk of GI bleeding compared to warfarin (Abraham et al, 2017; Halvorsen et al, 2017).

No ischaemic outcomes including ischaemic or haemorrhagic stroke or systemic embolism were reported in the present study. These results are conflicting with the ROCKET-AF trial, where combined incidence of stroke and systemic embolism was 2.4% per year for warfarin and 2.1% per year for rivaroxaban (Patel et al, 2011). Other studies also show conflicting results to those reported in the present study (Mao et al, 2014; Yao et al, 2016; Halvorsen et al, 2017). Similarly to bleeding incidence, this difference may be attributed to the small sample size and lack of patient follow-up after recruitment.

Most studies show that NOACs are associated with similar risks of stroke and systemic embolism compared to warfarin (Graham et al, 2016; Kwon et al, 2016; Larsen et al, 2016; Noseworthy et al, 2016). However, studies have also reported that apixaban is associated with reduced risk of stroke or systemic embolism compared to warfarin (Yao et al, 2016) and that dabigatran, rivaroxaban and apixaban are associated with reduced stroke or systemic embolic events compared to warfarin (Ruff et al, 2014).

Recent studies adopt the CHA_2DS_2-VASc scoring system to assess stroke risk (Yao et al, 2016; Coleman and Bunz, 2017). The study cohort did not differ significantly ($p>0.05$) in CHA_2DS_2-VASc score, with a mean CHA_2DS_2-VASc of 2.02 in patients taking warfarin and 2.20 in patients taking rivaroxaban, indicating no preference in anticoagulant treatment

related to stroke risk. Peacock et al (2017) have also shown higher CHA$_2$DS$_2$-VASc scores to be associated with increased incidence of major bleeding.

Regular INR monitoring to assess TTR can be burdensome, time-consuming and costly, yet is indispensable for patients on warfarin therapy (Finkelman et al, 2014). TTR is a reliable probability indicator for both bleeding and other thromboembolic events. (Bjorck et al, 2016). Studies have reported that patients with a TTR of 70% or greater or low INR variability have a significantly lower incidence of treatment complications, including bleeding and ischaemic outcomes, compared with those with TTR below 70% (Cotte et al, 2014; Bjorck et al, 2016; Chan et al, 2016; Grzymala-Lubanski et al, 2017).

In the present study the mean TTR for patients on warfarin was 63% according to the Rosendaal Linear Interpolation Method. These results are similar to TTR reported in clinical trials, including the RE-LY trial (64%), RE-COVER trial (60%) and ARISTOTLE trial (62%) (Connolly et al, 2009; Schulman et al, 2009; Granger et al, 2011). Results from other retrospective studies carried out in Portugal and USA have also reported similar results, with a mean TTR of 60% and 65% respectively (Caldeira et al, 2014; Pokorney et al, 2015).

Pharmacist intervention in anticoagulation clinics as part of a multidisciplinary team has been reported to improve INR control, TTR, identify and resolve medication-related problems and decrease adverse events, leading to reduction in hospital admissions and decreased healthcare costs (Bungard et al, 2009; Wieloch et al, 2011; Young et al, 2011; Dib et al, 2014; Harrison et al, 2015; Patel et al, 2016).

Polypharmacy was evident in the patient population studied, with most patients taking between 5 and 8 chronic medications daily. Polypharmacy increases bleeding risk in patients with AF and VTE (Leiss et al, 2014; Wang et al, 2016). A post-hoc analysis of the ROCKET-AF trial, compared warfarin and rivaroxaban bleeding in relation to polypharmacy, showing that the risk of major bleeding was lower for rivaroxaban in patients taking less than 5 medications. Similar rates of bleeding were observed between warfarin and rivaroxaban groups in patients taking more than 5 medications (Piccini et al, 2016).

Polypharmacy has also been shown to increase the likelihood of DDIs (Guthrie et al, 2015; Rodrigues and Oliveira, 2016). In the present study, the drugs associated with potential DDIs for patients on warfarin included simvastatin, amiodarone and omeprazole. These results are comparable to other studies where simvastatin and amiodarone are the most common DDIs associated with warfarin treatment (Gavronski et al, 2012; Guidoni et al, 2016). Evidence shows that the DDI between warfarin and simvastatin is clinically significant and unique to carriers of the CYP2C9*3 allele (Andersson et al, 2012). This highlights the importance of genotyping to guide warfarin dosing. A randomised trial carried out by Pirmohamed et al (2013) showed that genotype-based dosing at the initiation of warfarin therapy increased TTR, decreased period of time to reach a stable warfarin dose and therapeutic INR, and decreased the number of warfarin dose adjustments. Other observational studies are consistent with these findings (Jorgensen et al, 2012; Yang et al, 2013; Elliott et al, 2017). Alternative statins such as atorvastatin, fluvastatin and rosuvastatin cannot be considered since

interaction with warfarin has also been reported (Maji et al, 2013; Zhelyazkova-Savova et al, 2014).

With respect to amiodarone a significant DDI with warfarin has been reported (McDonald et al, 2012). Santos et al. (2014) stated that concomitant use of these amiodarone and warfarin is not associated with adverse effects but influences the maintenance dose of warfarin. Flaker et al. (2014) concluded different results, showing an increased risk of stroke and systemic embolism and lowering of TTR with concomitant use of warfarin and amiodarone. A DDI between warfarin and omeprazole has also been reported. Alternative proton pump inhibitors to omeprazole, such as pantoprazole and lansoprazole, could be considered since they interact less with warfarin (Wedemeyer and Blume, 2014; Henriksen et al, 2015).

The drugs identified as resulting in potential DDIs in patients on rivaroxaban were amiodarone, paroxetine and verapamil. DDIs with amiodarone and verapamil in relation to rivaroxaban may result in cases of reduced renal function, where decreased drug clearance results in increased risk of bleeding. Bel'diev (2016) has shown that dose reduction of rivaroxaban in patients with reduced renal clearance can significantly reduce such DDIs. Paroxetine is an inhibitor of CYP450, an enzyme involved in the rivaroxaban metabolism pathway and concomitant use of paroxetine with rivaroxaban should be avoided (Kapil et al, 2015). Other antidepressants which have less CYP450 inhibition such as citalopram, venlafaxine and mirtazapine are safer (Allen et al, 2013; Aguiar, 2016).

Non-adherence to medications is a growing concern for healthcare systems as it is associated with a higher incidence of adverse health outcomes and imposes a greater financial burden on healthcare systems (Ho et al, 2009; Iuga and McGuire, 2014). In the present study there was a significant different ($p<0.001$) in adherence rates between warfarin and rivaroxaban patients, with patients in the rivaroxaban group having a significantly higher level of adherence to treatment. Results are comparable to other studies that report higher adherence rates to rivaroxaban compared to warfarin (Laliberte et al, 2014; Nelson et al, 2015; Beyer-Westendorf et al, 2015; Camm et al, 2015; Hecker et al, 2016) When comparing adherence rates between different NOACs, adherence was observed to be highest in patients taking rivaroxaban (Forslund et al, 2015; McHorney et al, 2015; Brown et al, 2016; Coleman et al, 2016b; Yao et al, 2016).

Adherence may be affected by numerous factors, including gender, age, level of education, living situation, drug and alcohol abuse, cost of treatment and other comorbidities, amongst other factors (Cruess et al, 2010; Mathes et al, 2014; Mayet, 2015; Pandya et al, 2017).

Studies reporting the association between gender and adherence to anticoagulation concluded that female gender is a predictor for higher adherence (Kneeland and Fang, 2010; Castellucci et al, 2015). In the present study, association between gender and adherence to warfarin and rivaroxaban was not statistically significant ($p>0.05$).

Non-adherence to medication has been reported in all age groups, however the elderly are more prone to this phenomenon due to a possible decline in physical and cognitive function, other comorbidities and polypharmacy (Campbell et al, 2012; Yap et al, 2016).

The majority of studies report younger patients as having lower adherence rates to warfarin (Kneeland and Fang, 2010; Mangnall et al, 2016; Mayet, 2016). Findings from the present study demonstrated the contrary, where adherence to warfarin was statistically higher in the younger age group (p<0.05). Studies have reported that patients on rivaroxaban are more adherent to treatment with increasing age (Brown et al, 2016; Lai et al, 2016) Results obtained in the present study show that adherence to rivaroxaban was similar in different age groups (p>0.05).

Lower levels of education have been shown to affect adherence to warfarin therapy (Davis et al; Kimmel et al, 2007; Cruess et al, 2010; Raparelli et al, 2017). Findings from the present study similarly demonstrated that warfarin adherence is lower in patients with primary level education and the association was statistically significant (p<0.05). Adherence to rivaroxaban was similar among different education levels (p>0.05).

Warfarin and rivaroxaban are associated with significant bleeding risk, which is reported to be a predictor of non-adherence and discontinuation (Garkina et al, 2016; Loewen et al, 2016; Yao et al 2016). The relationship between incidence of bleeding and adherence rates was assessed in this study with no significant association observed (p>0.05). This result could be due to the small sample size.

Studies have reported that polypharmacy is associated with several negative clinical outcomes, including non-adherence (Marcum et al, 2012; Cadogan et al, 2016; Zelko et al, 2016). In the present study, when correlating the number of medications with adherence score, there was no statistically significant association (p>0.05).

Adherence to treatment was inversely proportional to the cost of treatment. Patients on rivaroxaban had higher adherence rates compared to warfarin. A reason for this could be, that since rivaroxaban is not available on the GFL and has to be purchased out-of-pocket, patients might be more inclined to adhere to treatment. At the time of the study and to the author's best knowledge, no other publications comparing cost of anticoagulants and adherence have been carried out.

Several pharmacoeconomic analysis, mainly using Markov models, have been conducted to compare the cost-effectiveness of NOACs to warfarin in patients with non-valvular AF and VTE.

Dabigatran has been shown to be a cost-effective option to warfarin in patients with non-valvular AF and VTE in the USA (Freeman et al, 2011; Shah et al, 2011; Kamel et al, 2012b; You et al, 2012; Clemens et al, 2014), Canada (Sorensen et al 2011; Nshimyumukiza et al, 2013; Singh et al, 2013), the UK (Pink et al, 2011; Kansal et al, 2012; Jugrin et al, 2015), Europe (Davidson et al, 2012; Gonzalez-Juanatey JR et al, 2012; Andrikopoulos et al, 2013; Pletscher et al, 2013; Wouters et al, 2013; Galvani et al, 2015; Van Leent et al, 2015; Stevanovic et al, 2016), Brazil (Souza et al, 2015), Hong Kong (Chang et al, 2013) and South Africa (Bergh et al, 2013).

Studies comparing rivaroxaban to warfarin in non-valvular AF and VTE have reported that rivaroxaban is a cost-effective option in the USA (Lee et al, 2012; Seaman et al, 2013), the UK (Bamber et al, 2016; Crowther and Cuker, 2017), Europe (Kleintjens et al, 2013; Kourlaba et al, 2014; Morais et al, 2014; Mensch et al, 2015; Rubio-Terres et al, 2016), China (Zhou et al, 2016), Japan (Hori et al, 2016) and Singapore (Wang et al, 2014).

Apixaban was reported to be a cost-effective alternative to warfarin in non-valvular AF and VTE in the USA (Kamel et al, 2012a; Lee et al, 2012), the UK (Dorian et al, 2014; Lanitis et al, 2017), Europe (Rudakova and Parfenov et al, 2014; Stevanovic et al, 2014; Esquivias et al, 2015; Hallinen et al, 2016; Pinyol et al, 2016), Argentina (Giorgi et al, 2015); Australia (Ademi et al, 2013), and China (Li et al, 2016). Edoxaban has been reported to be a cost-effective option to warfarin in non-valvular AF and VTE in the USA (Magnuson et al, 2015; Preblick et al, 2015; Miller et al, 2016; Nguyen et al, 2016), the UK (Taylor et al, 2015), and in Europe (Krejczy et al, 2015; Rognoni et al, 2015).

Conflicting reports exist as regards which NOAC is more cost-effective in non-valvular AF. Sorensen et al (2012), Coyle et al (2013), Kansal et al (2013), Zheng et al (2014) and Schoenherr et al (2016) reported that dabigatran is economically-dominant over rivaroxaban in a USA, Canadian, UK and Spanish setting respectively. Conversely, Edwards et al (2011), Lanitis et al (2014b) and Wang et al (2016) reported rivaroxaban to be economically-dominant over dabigatran in the UK, France and Singapore respectively. In a UK (Lip et al, 2014; Rudakova and Tatarskii, 2014) and Greek setting (Athanasakis et al, 2015), apixaban was reported to be a cost-effective alternative to dabigatran and rivaroxaban. Amin et al (2015), Lip et al (2015) and Tanaka et al (2015) reported that apixaban is more cost-effective than dabigatran, rivaroxaban and edoxaban in a USA, UK and Brazilian setting respectively. Edoxaban was reported to be more cost-effective than rivaroxaban in a USA setting (Miller et al, 2016).

A systematic review of 16 economic analyses reported that NOACs are economically-dominant over low molecular-weight heparins in VTE, while comparison between

NOACs showed dabigatran to be the least cost-effective option and rivaroxaban as the most cost-effective option (Brockbank and Wolowacz, 2017).

A direct pharmacoeconomic Markov model could not be carried out since only rivaroxaban 10mg was available on the GFL at the time of the study, hence no reference tender pricing for rivaroxaban 20mg was available. For this reason, a preliminary cost analysis was carried out and showed a significant difference in the cost of oral anticoagulants based on cost of treatment, INR monitoring and GP visits, with warfarin approximately one-fourth the cost of rivaroxaban. The reason for this significant difference in cost may be attributed to rivaroxaban 20mg and other NOACs not being available on the GFL and no tender pricing is available. Morevover since NOACs are still under patent, no cheaper generic alternatives are available.

The majority of patients in this study monitored their INR by means of a laboratory-based approach at the hospital ACC. The mean total cost per patient per month was significantly lower when INR was monitored via POC testing, imposing less financial burden on the government healthcare system. With POC INR testing, patients are given the INR result and warfarin prescription within minutes. This system also allows face-to-face discussion of the INR result and dose with the physician and reduces waiting time and overcrowding at the ACC. This approach may lead to a decrease in dose/administrative errors which may occur when INR results and dose are communicated via telephone. Moreover, POC testing requires a smaller amount of blood, obtained via a finger prick test, making the procedure less invasive compared to taking a venous blood sample.

4.2 Study limitations

The following study limitations were identified. The results obtained and correlations performed may have been limited due to the small sample size. This limitation is due to the small number of patients taking NOACs at the time of recruitment. Due to the short duration of the study, patient follow-up was not carried out. Convenience sampling and self-reported adherence to treatment may create bias and errors in the results. Using administrative data has limitations when conducting cost analysis. Costs of data obtained may not necessarily be up-to-date, data can be misclassified and relevant information may not be available. Indirect costs such as bleeding episodes and ischaemic outcomes requiring hospital admission were not calculated. Productivity loss costs and travelling expenses associated with INR monitoring were not calculated. Pharmacist intervention was not assessed in this study.

4.3 Recommendations for further study

The patients recruited may be followed-up and prospective studies with a larger patient cohort could be undertaken to confirm the findings of this study. Adherence rates can be assessed using a more direct approach, such as monitoring blood and urine drug levels or by assessing the rates of prescription refills. A Markov model could be developed to carry out a full pharmacoeconomic evaluation. Further studies assessing pharmacist intervention in patient counselling and education, drug therapy monitoring and communication between members of the multidisciplinary team could be carried

out. Studies assessing patient and physician attitudes and knowledge on anticoagulation treatment could be carried out.

4.4 Conclusions

The findings of this study have implications for rivaroxaban (NOAC) use in Malta. From an efficacy and safety perspective it was demonstrated that rivaroxaban is associated with lower incidence and severity of bleeding, higher adherence rates and fewer potential DDIs. From a cost analysis perspective it has been demonstrated that rivaroxaban is substantially more expensive than warfarin. A reason for this significant difference in cost is since rivaroxaban 20mg and other NOACs are not available on the GFL and all NOACs are still on patent, hence no cheaper generic alternatives are available. Introducing rivaroxaban 20mg or another NOAC on the GFL in Malta can be a viable personalised treatment option for patients who are non-adherent and not controlled on warfarin therapy. These include patients who need frequent INR monitoring, have a high percentage of INR tests which are out-of-range and have increased episodes of bleeding.

4.5 Dissemination of results

An abstract titled 'Drug interactions and bleeding complications with rivaroxaban compared to warfarin' was presented as a poster presentation at the 77th International Pharmaceutical Federation World Congress of Pharmacy and Pharmaceutical Sciences, Seoul, Republic of Korea, 10-14 September 2017 (Appendix 7).

An abstract titled 'Impact of Rivaroxaban in Cardiovascular Disease' was presented as an oral poster discussion presentation at the 46th ESCP Symposium on Clinical Pharmacy, Heidelberg, Germany, 9-11 October 2017 (Appendix 7).

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Appendices

Appendix 1: Validation form

Instructions to Validation Panel

The patients will be recruited from MDH and community pharmacies. Data will be collected via semi-structured patient interview and viewing of patient hospital related documentation. The data will be collected and filled in by the researcher and not the patient.

The Patient Data Collection Form is divided into five sections. For each question in each section, please grade the relevance of the question from lowest to highest (1-5), the level of agreement with the options given from lowest to highest (1-5) and any comments/remarks or general improvements which should be addressed.

Patient Data Collection Form

Section A: Patient Details

Question	Relevance of question (1 to 5) (lowest-highest)	Level of agreement with options included (1 to 5) (lowest-highest)	Remarks
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			

Section B: Current Anticoagulation Therapy

Question	Relevance of question (1 to 5) (lowest-highest)	Level of agreement with options included (1 to 5) (lowest-highest)	Remarks
11			
12			
13			
14			
15			
16			
17			
18			
19			

Section C: History of Anticoagulation Therapy

Question	Relevance of question (1 to 5) (lowest-highest)	Level of agreement with options included (1 to 5) (lowest-highest)	Remarks
20			
21			
22			
23			
24			
25			
26			

Section D: Current Medications

Question	Relevance of question (1 to 5) (lowest-highest)	Level of agreement with options included (1 to 5) (lowest-highest)	Remarks
27			

Section E: Adherence to Anticoagulant Therapy

Question	Relevance of question (1 to 5) (lowest-highest)	Level of agreement with options given (1 to 5) (lowest-highest)	Remarks
i			
ii			
iii			
iv			
v			
vi			
vii			
viii			
ix			

Appendix 2: Validation results

Section	Question	Relevance		Level of Agreement with Options given	
		Mean Score	Range	Mean Score	Range
A	1. Patient study number	4.0	2-5	N/A	N/A
	2. Telephone/Mobile number	4.0	2-5	N/A	N/A
	3. Gender	4.3	2-5	N/A	N/A
	4. Age	4.7	4-5	N/A	N/A
	5. Consultant	4.1	3-5	4.6	4-5
	6. Patient recruitment	4.9	4-5	N/A	N/A
	7. Level of education	4.7	4-5	4.6	4-5
	8. Living situation	4.8	4-5	4.7	4-5
	9. Smoking	4.1	2-5	4.1	3-5
	10. Alcohol consumption	4.5	3-5	4.8	4-5
B	11. Prescribed anticoagulant	5.0	5-5	5.0	5-5
	12. Dosage and frequency of anticoagulant administration	4.8	3-5	4.7	3-5
	13. Indication for anticoagulation therapy	3.9	2-5	3.7	2-5
	14. Start date of anticoagulant	4.7	3-5	4.4	3-5
	15. Given option to take NOAC instead of warfarin	4.5	2-5	4.4	2-5
	16. Prior knowledge about NOACs	4.8	3-5	4.4	3-5
	17. Monitoring of INR	4.9	4-5	4.7	4-5
	18. Inconvenience of regular INR monitoring	4.8	3-5	4.0	3-5
	19. INR results	3.9	1-5	3.7	1-5
C	20. Complications since treatment initiation	5.0	5-5	5.0	5-5
	21. Emergency admissions to hospital related to anticoagulant therapy	5.0	5-5	5.0	5-5
	22. Length of stay in hospital related to anticoagulant therapy	5.0	5-5	5.0	5-5
	23. Visits to GP related to anticoagulant therapy	5.0	5-5	5.0	5-5
	24. Adverse-effects related to anticoagulant therapy	5.0	5-5	5.0	5-5
	25. Incidence of bleeding related to anticoagulant therapy	4.9	4-5	4.7	2-5
	26. Type of bleeding	4.3	3-5	4.2	2-5
D	27. List of current medications	5.0	5-5	5.0	5-5

Section	Question	Relevance		Level of Agreement with Options given	
		Mean Score	Range	Mean Score	Range
E	i. Do you take your prescribed warfarin/rivaroxaban?	5.0	5-5	5.0	5-5
	ii. Do you take warfarin/rivaroxaban at their prescribed times?	5.0	5-5	5.0	5-5
	iii. If you travel abroad, do you take along warfarin/rivaroxaban?	5.0	5-5	5.0	5-5
	iv. Were there any occasions were you stopped taking warfarin/rivaroxaban out of your own free will?	5.0	5-5	5.0	5-5
	v. Did you ever miss a dose?	5.0	5-5	5.0	5-5
	vi. Did you miss/stop treatment because you forgot?	5.0	5-5	5.0	5-5
	vii. Did you miss/stop treatment, because you experienced adverse effects?	5.0	5-5	5.0	5-5
	viii. Did you miss/stop warfarin/rivaroxaban, because you have too many medicines and you got confused on how they should be administered?	5.0	5-5	5.0	5-5
	ix. Did you miss/stop treatment, because you felt good and decided that you did not need the medicine?	5.0	5-5	5.0	5-5

Appendix 3: Data collection form

Patient Data Collection Form

The Impact of a Direct Oral Anticoagulant in Cardiovascular Disease

PharmD Student – Mark-George Cardona

Date of Recruitment:

Section A: Patient Details

1. Patient Study Number:

2. Telephone/Mobile Number:

3. Gender: Male/Female

4. Age:

5. Consultant:

6. Patient recruitment:

- Cardiac Outpatients
- Neurology Outpatients
- Outpatient Anticoagulant Clinic
- Community Pharmacy – Please Specify _____
- Health Centre

7. Level of Education – Up to:

- Primary
- Secondary
- Post-Secondary
- Tertiary

8. Living Situation:

- Live alone
- Live with partner/family/friends
- Live in a nursing home/care facility

9. Smoking:

- Yes
- No

10. Alcohol Consumption:

- None
- Few drinks per week
- 1-2 units a day
- 3-4 units a day
- 5 or more units a day

Section B: Current Anticoagulation Therapy

11. Prescribed Anticoagulant:

- Warfarin
- Rivaroxaban
- Dabigatran
- Apixaban

12. Dosage and Frequency of Anticoagulant Administration:

Anticoagulant	Current Dose	Frequency

13. Indication for Anticoagulation Therapy:

- Ischaemic Stroke
- Atrial Fibrillation
- Myocardial Infarction
- Venous Thromboembolism
- Prosthetic Heart Valves
- Pulmonary Embolism
- Valvular Heart Disease
- Transient Ischaemic Attacks
- Antiphospholipid Syndrome

14. Start date of Anticoagulant:

15. Given option to take a NOAC instead of warfarin:

- Yes
- No

16. Prior knowledge about NOACs

- Rivaroxaban – Please Specify from where _____
- Dabigatran – Please Specify from where _____
- Apixaban – Please Specify from where _____

17. Monitoring of INR:

- **Health Centre (Point of Care Testing)**
- **Outpatient ACC Clinic**

18. Inconvenience of regular INR monitoring:

- **Yes**
- **No**

19. INR Results: (Up to 6 months since recruitment)

Date	INR Result	Dose

Section C: History of Anticoagulation Therapy

20. Complications since treatment Initiation:

- Bleeding
- Stroke
- Systemic Embolism
- Myocardial Infarction (MI)
- Other Ischaemic/Thrombotic Complications
- No Complications

21. Emergency admissions to hospital related to anticoagulant therapy:

- Yes
- No

22. If yes, length of Stay in Hospital Related to Anticoagulant Therapy:

23. Visits to GP related to the Anticoagulant Therapy:

- 0
- 1
- 2
- 3
- 4
- 5

24. Adverse-Effects since related to the anticoagulant therapy (Please Specify):
Examples Warfarin: Dizziness/Weakness, Bruising, Bleeding, Severe Headache or stomach pain, Diarrhoea, Vomiting, Fever
Examples Rivaroxaban: Back Pain, Bleeding, Dizziness, Headache, Itchiness, Numbness, Pins and Needles, Pain in the arms and legs

25. Incidence of bleeding related to the anticoagulant therapy:

- 0
- 1
- 2
- 3
- >3

26. Type of bleeding - (BARC) Criteria:

- **Type 0**
- **Type 1**
- **Type 2**
- **Type 3**
- **Type 4**
- **Type 5**

Section D: Current Medications

27. List of Current Medications:

Generic Name	Dose	Dosage Regimen

Section E: Adherence to Anticoagulantion Therapy:

Question	Never	Rarely	Occasionally	Sometimes	Often	Always
i. Do you take warfarin/rivaroxaban?	0	1	2	3	4	5
ii. Do you take warfarin/rivaroxaban at their prescribed times?	0	1	2	3	4	5
iii. If you travel abroad, do you take along warfarin/rivaroxaban?	0	1	2	3	4	5
iv. Were there any occasions were you stopped taking warfarin/rivaroxaban out of your own free will?	5	4	3	2	1	0
v. Did you ever miss a dose?	5	4	3	2	1	0
vi. Did you miss/stop treatment because you forgot?	5	4	3	2	1	0
vii. Did you miss/stop treatment, because you experienced adverse effects?	5	4	3	2	1	0
viii. Did you miss/stop warfarin/rivaroxaban, because you have too many medicines and you got confused on how they should be administered?	5	4	3	2	1	0
ix. Did you miss/stop treatment, because you felt good and decided that you did not need the medicine?	5	4	3	2	1	0

Appendix 4: Patient consent form in English and Maltese

I am a Maltese citizen and am over eighteen (18) years of age.

I have been asked to participate in a research study entitled:

'Pharmacoeconomics of Innovative medicines in Cardiovascular Disease'

The purpose and details of the study have been explained to me by   Mark-George Cardona

and any questions which I raised have been adequately clarified.

I give my consent to the Principal Researcher to make the appropriate observations.

I understand that the results of this study may be used for medical or scientific purposes and that the results achieved from the study in which I am participating may be reported or published. However, I shall not be personally identified in any way, either individually or collectively, without my expressing written permission.

I am under no obligation to participate in this study and am doing so voluntarily.

I may withdraw from the study at any time, without giving any reason. This will not affect in any way the care and attention and treatment normally given to me *(applicable only in case of patients receiving treatment).*

I am/**I am not** receiving any remuneration for participating in this study.

In case of queries during the study I may contact on
mark.cardona.08@um.edu.mt/99009087

Signature of participant   _____

Name of participant   _____

ID of participant   _____

Signature of Chief Researcher   _____

Name of Chief Researcher   Mark-George Cardona

ID of Chief Researcher   301190M

Date

Jien/a ċittadin/a Malti/ja u għalaqt tmintax (18)-il sena.

Talbuni biex nieħu sehem fi studju riċerka bl-isem ta':

'**Pharmacoeconomics of Innovative medicines in Cardiovascular Disease**'

Il-għan u d-dettalji ta' l-istudju spejgathomli   Mark-George Cardona

li wkoll iċċaratli xi mistoqsijiet li għamilt.

Nagħti l-kunsens tiegħi lill-persuna responsabbli għal-din ir-riċerka u l-assistenti tagħha biex jagħmlu l-osservazzjonijiet li hemm bżonn.

Jiena nifhem li r-riżultati ta' dan l-istudju jistgħu jintużaw għal skopijiet xjentifiċi u jista' jiġi ppubblikat rapport bil-miktub: jekk isir hekk b'ebda mod ma nista' nkun identifikat/a, individwalment jew bħala parti minn grupp, mingħajr il-kunsens tiehħi bil-miktub.

Jiena ma għandi l-ebda dmir li nieħu sehem f'dan l-istudju u dan qed nagħmlu minn rajja.

Jiena nista', meta rrid, ma nkomplix nieħu sehem fl-istudju, u mingħajr ma' nagħti raġuni. Jekk nagħmel hekk xorta nibqa' nieħu l-kura li ssoltu tingħatali (*tapplika biss għal pazjenti li qed jieħdu kura*).

Jiena qed nitħallas**/mhux qed nitħallas** biex nieħu sehem f'dan l-istudju.

Jekk ikolli xi diffikulta' waqt l-istudju, nista' nistaqsi għal:
mark.cardona.08@um.edu.mt/99009087

Firma tal-parteċipant   _____

Isem tal-parteċipant   _____

Numru ta' l-identita   _____

Firma tal-persuna responsabbli għal din ir-riċerka   _____

Isem tal-persuna responsabbli għal din ir-riċerka   Mark-George Cardona

Numru ta' l-identita   301190M

Data

Appendix 5: Patient information sheet in English and Maltese

I Mark-George Cardona am a pharmacist, currently undertaking a research project as part of my Doctorate in Pharmacy entitled '**Pharmacoeconomics of Innovative Medicines in Cardiovascular Disease'** under the principal supervision of Prof. Anthony Serracino-Inglott and Dr. Francesca Wirth from the Department of Pharmacy at the University of Malta.

You have been identified to participate in this research which involves the following:

Aim of research and how will you benefit?

Warfarin/rivaroxaban/dabigatran/apixaban are anticoagulants (drugs which thin the blood) normally used in the prevention of thrombosis and thromboembolism (formation of blood clots in the blood vessels and their migration elsewhere in the body). You will be interviewed to determine your adherence to warfarin, rivaroxaban, dabigatran or apixaban, assess potential side-effects such as bleeding, and identify drug-drug interactions. INR control will also be assessed if you are taking warfarin. This research will determine if rivaroxaban/dabigatran/apixaban is more suitable and cost-effective compared to warfarin.

Your involvement

You will be recruited from Cardiology outpatients, ACC clinic or community pharmacy and a data collection form will be completed at time of recruitment via patient interview and viewing of your hospital documentation.

Other important information

Participation in this research is entirely voluntary. The researcher will access your hospital files to obtain data required for this study. The information accessed will be kept strictly confidential and used solely for the purpose of the research according to the Data Protection Act. Refusal to participate will in no way affect the treatment you receive as a patient at Mater Dei Hospital or in the community. You may discontinue participation in this research at any time without any prejudice.

Kindly sign the attached consent form if you agree to participate in this research.

Thank you in advance for your cooperation.

Mark-George Cardona MPharm

mark.cardona.08@um.edu.mt

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Jiena Mark-George Cardona spiżjar, qiegħed nagħmel proġett ta' riċerka bħala parti mill-istudju tiegħi għal Dottorat fil-Farmaċija. Dan l-istudju huwa intitolat **'Pharmacoeconomics of Innovative Medicines in Cardiovascular Disease'.** Dan l-istudju qiegħed jiġi mmexxi bis-superviżjoni prinċipali tal-Professur Anthony Serracino-Inglott u Dr.Francesca Wirth mid-Departiment tal-Farmacija fl-Universita ta' Malta.

Inti ġejt identifikat/a biex tipparteċipa f'din ir-riċerka li tinvolvi dan li ġej:

L-għan tar-riċerka u l-benefiċċju għalik

Il-warfarina/rivaroxaban/dabigatran/apixaban huma mediċini li inti qed tieħu biex traqqaq id-demmu jintużaw biex inaqsu ir-riskju/jiprevenu trombosi. Waqt dan l-istudjuinti ħa tiġi osservat/a biex jiġi dditerminat jekk tiħux dawn il-pilloli kif suppost. Il-kontrol ta' l-INR ħa tiġi evalwata wkoll jekk inti qed tieħu l-warfarina. Din ir-riċerka se tiddetermina jekk il-mediċini ġodda li jeżistu biex iraqqu d-demm għandhomx xi vantaġġ fuq il-warfarina.

L-involviment tiegħek

Inti ha tkun magħżul min l-"Outpatients" tal-Kardjoloġi u min l-ACC clinic jew spiżerija tal-komunita biex tieħu sehem f'dan l-istudju. X' informazzjoni oħra ħa tiġi miġbura mil-file personali tiegħek.

Tagħrif ieħor importanti

Il-parteċipazzjoni tiegħek f'din din ir-riċerka hija kompletament volontarja. Ir-riċerkatur ħa jkollu aċċess għal fajls tiegħek sabiex jiġbor informazzjoni meħtieġa f'din ir-riċerka. It-

tagħrif miġbur jinżamm kunfidenzjali u jintuża biss għall-finijiet tal-proġett skont l-Att dwar il-Protezzjoni tad-Data. Jekk tirrifjuta li tipparteċipa, dan bl-ebda mod ma jaffetwa t-trattament li tirċievi bħala pazjent/a fl-Isptar Mater Dei jew fl-ispiżerija. Tista', f'kull waqt u mingħajr preġudizzu, twaqqaf il-parteċipazzjoni tiegħek f'dan il-proġett.

Int ġentilment mitlub/a tiffirma l-formola ta' kunsens mehmuża jekk taċċetta li tipparteċipa f'din ir-riċerka.

Grazzi bil-quddiem għall-kooperazzjoni tiegħek.

Mark-George Cardona MPharm

mark.cardona.08@um.edu.mt

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Appendix 6: Ethics approval

L-UNIVERSITÀ TA' MALTA
Msida - Malta
SKOLA MEDIKA
Sptar Mater Dei

UNIVERSITY OF MALTA
Msida - Malta
MEDICAL SCHOOL
Mater Dei Hospital

Ref No: **19/2016**

Friday 15th April 2016

Mr Mark-George Cardona
66, The Keep
Triq Dun Gwann Theuma
Attard, ATD2062

Dear Mr Mark-George Cardona,

Please refer to your application submitted to the Research Ethics Committee in connection with your research entitled:

Pharmacoeconomics of Innovative medicines in Cardiovascular Disease

The University Research Ethics Committee granted ethical approval for the above mentioned protocol.

Yours sincerely,

Dr. Mario Vassallo
Chairman
Research Ethics Committee

Appendix 7: Dissemination of results

FIP Abstract Submission

Pharmaceutical sciences

Pharmacy practice research

FIP-677

Drug interactions and bleeding complications with rivaroxaban compared to warfarin

Mark G. Cardona, Francesca Wirth, Anthony Serracino-Inglott[*], Lilian M Azzopardi

My preferred method of presentation is: Poster Presentation

Background: Compared to warfarin, the novel oral anticoagulant (NOAC) rivaroxaban has fewer potential drug-drug interactions (DDIs). However, there is conflicting evidence regarding bleeding complications.

Purpose: To compare rivaroxaban and warfarin with respect to potential DDIs and incidence and severity of bleeding.

Methods: Following ethics approval, 100 patients (50 rivaroxaban, 50 warfarin) were recruited by convenience sampling from hospital outpatient clinics and community pharmacies. Time in therapeutic range for warfarin was calculated using the Rosendaal Linear Interpolation Method. The Bleeding Academic Research Consortium (BARC) criteria were used to classify bleeding complications.

Results: Patients in the rivaroxaban and warfarin group were comparable (p>0.05) for age (mean 65 years, range 27-85), gender (53 female, 47 male), indication for anticoagulation (59 atrial fibrillation, 30 deep vein thrombosis) and mean duration of anticoagulation use (10 months, range 1-33). A total of 19 (mean 0.4/patient, range 0-2) and 91 (mean 1.8/patient, range 0-4) DDIs were identified in patients on rivaroxaban and warfarin respectively ($X^2(4)=47.81$, p<0.001). A total of 768 INR tests were processed in a 6-month period, of which 37% were not in therapeutic range. Twenty-four patients reported BARC Type 1 bleeding (6 rivaroxaban, 18 warfarin) and 10 patients reported Type 2 bleeding (4 rivaroxaban, 6 warfarin) ($X^2(4)=10.17$, p<0.001).

Conclusion: A higher risk of DDIs and increased bleeding complications were observed in patients on warfarin. NOACs provide a personalised treatment option for patients not stable on warfarin.

ESCP Abstract Submission

Pharmacotherapy

ESCP17SY-1394

Impact of Rivaroxaban in Cardiovascular Disease

Mark G. Cardona, Francesca Wirth[*], Anthony Serracino-Inglott, Robert G Xuereb Lilian M Azzopardi

Please specify your abstract type: Research Abstract

Background and Objective: Compared to warfarin, the novel oral anticoagulant rivaroxaban has uncomplicated dosing with no need for INR monitoring and fewer drug and food interactions, which have been reported to improve adherence to treatment. The objectives were to determine INR control for patients on warfarin and compare warfarin and rivaroxaban with respect to treatment adherence, incidence and severity of bleeding and drug-drug interactions (DDIs).

Setting and Method: Following ethics approval, 100 patients (50 warfarin, 50 rivaroxaban) were recruited by convenience sampling from hospital outpatient clinics and community pharmacies. Time in therapeutic range (TTR) was calculated using the Rosendaal Linear Interpolation Method. The validated treatment adherence questionnaire by Anastasi et al[1] was adapted to assess therapy adherence. The Bleeding Academic Research Consortium (BARC) criteria were used to classify severity of bleeding complications. Micromedex Complete Drug Interactions and Medscape Multi-Drug Interaction Checker tools were used to assess DDIs.

Main outcome measures: TTR; treatment adherence; bleeding complications; DDIs

Results: Patients in both groups were comparable ($p > 0.05$) for age (mean 65 years, SD 12.91), gender (53 female, 47 male), indication for anticoagulation (59 atrial fibrillation, 30 deep vein thrombosis) and mean duration of anticoagulation use (10 months, SD 5.97). Over a 6-month period, 768 INR tests were processed (mean 2.56 tests/patient/month, SD 1.58), of which 37% were not in TTR. Patients on rivaroxaban obtained a significantly higher mean adherence score (44 out of 45, SD 1.41) compared to patients on warfarin (41 out of 45, SD 3.92) (U=719.5, $p < 0.001$). Twenty-four patients reported BARC Type 1 bleeding (18 warfarin, 6 rivaroxaban) and 10 patients reported Type 2 bleeding (6 warfarin, 4 rivaroxaban) ($X^2(4)=10.17$, $p < 0.001$). A total of 91 (mean 1.8/patient, SD 1.03) and 19 (mean 0.4/patient, SD 0.52) potential DDIs were identified in patients on warfarin and rivaroxaban respectively ($X^2(4)=47.81$, $p < 0.001$). Simvastatin (23), amiodarone (12) and omeprazole (11) were the drugs involved in the highest number of potential DDIs with warfarin. Amiodarone (7), paroxetine (3) and verapamil (3) were the drugs involved in the highest number of potential DDIs with rivaroxaban.

Conclusion: Patients on warfarin were less adherent to treatment, had a higher incidence of BARC Type 1 and 2 bleeding and a greater potential for DDIs compared to rivaroxaban.

1.Anastasi A et al. CP-185: An innovative treatment adherence tool. Eur J Hosp Pharm 2017;24:A83.

Disclosure of Interest: None Declared