Aspirin and Novel Oral Anticoagulants: Reporting of Adverse Drug Reactions

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It is with genuine gratefulness that I dedicate this thesis to my parents for their encouragement during my years of study. To my sisters for their continuous support throughout my studies.

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Abstract

The introduction of the novel oral anticoagulants (NOACs) into clinical practice provided alternative options for thromboprophylaxis. The aims of the study were to carry out a comparative analysis of adverse drug reactions (ADRs) reported for aspirin and for NOACs, to identify studies on the use of NOACs in peripheral artery disease (PAD) and to analyse patient accessibility to NOACs. The methodology was divided into five phases. (1) Pharmacovigilance (PV) reports from Eudravigilance were used to analyse ADRs for aspirin and for thee NOACs (apixaban, dabigatran and rivaroxaban). Fifteen ADRs were chosen to be analysed for the four medications. Reported ADRs between the years 2013 and 2017 for the four drugs investigated were compared. (2) A questionnaire was developed and validated to collect information from the Maltese population on ADRs encountered while patients were taking aspirin or NOACs. Fifty patients were recruited for the study (25 patients on aspirin, 25 on rivaroxaban). (3) Documented ADRs from PV reports were compared to reported ADRs from patients. (4) A literature search was carried out to identify studies on the use of NOACs in off-label use for PAD. (5) Accessibility of NOACs was evaluated by using the local hospital formulary to identify which NOACs are procured through the National Health Service. Bleeding-related ADRs (38,826/51,391 or 75.6%) were the most frequently reported ADRs in PV reports, with gastrointestinal bleeding (N=25,892) being the most commonly frequently ADR for rivaroxaban (n=12,974), aspirin (n=5,855), dabigatran (n=5,321) and apixaban (n=1,742). Rivaroxaban had the largest number of reported cases of ADRs (n=24,832). For all fifteen ADRs investigated, statistically significant differences were observed between the four medications when comparing reported cases of ADRs. Thirty-six patients recruited for the questionnaire suffered at least one ADR following administration of either aspirin (18 patients) or rivaroxaban (18 patients). Bleeding-related ADRs, were the least reported

ADRs by the questionnaire respondents (11 for aspirin and 4 for rivaroxaban). Eight studies analysing the use of NOACs in PAD patients were identified. Rivaroxaban is the only NOAC which is procured through the Maltese National Health Service. Reflections on the findings of the study indicate that: (1) results from the questionnaire differ from results obtained from PV reports. Bleeding-related ADRs were highest in PV reports and were the lowest reported ADRs in patient questionnaires. The result may suggest an under-reporting of ADRs to PV databases which may be considered as minor or less serious when compared to bleeding-related ADRs. Result reflects a bias on the reporting of ADRs to PV databases. (2) The high number of reported ADRs for rivaroxaban compared to dabigatran and apixaban possibly reflect the consumption trends for rivaroxaban. From the three NOACs studied, dabigatran was the first NOAC which was approved for use. Consumption trends show that rivaroxaban is the most used NOAC. (3) Significant differences in ADRs reported for NOACs and aspirin could be due to consumption differences between medications, differences in safety profile or reporting bias. ADRs are more likely to be reported for novel medications such as NOACs which lack safety information as compared to the more conventional drugs such as aspirin. (4) Two identified studies show that when added to aspirin, NOACs have favourable efficacy outcomes compared to aspirin alone when used in PAD patients. (5) More data on the safety and efficacy of NOACs is necessary to help in determining the risk-benefit ratio of therapy.

Keywords: aspirin, novel oral anticoagulants, comparative analysis, adverse drug reactions, peripheral artery disease

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Glossary

Drug-event pair - combination of a medical product and an adverse drug reaction reported in an individual case safety report.[1]

Eudravigilance Data Analysis System (EVDAS) – a component of Eudravigilance which is used for pharmacovigilance safety monitoring activities. Used in signal detection and evaluation of individual case summary reports.[2]

Eudravigilance post-authorisation module (EVPM) - a collection of individual case summary reports related to all medicinal products authorised in the European Economic Area. Examples of individual case summary report in Eudravigilance post-authorisation module include; spontaneous reports, reports from studies.[3]

Eudravigilance Query Libraries – is a component of Eudravigilance data analysis system and contains a number of sections which can be used to analyse adverse drug reactions eg. Pharmacovigilance query library.

Individual Case Line Listing (ICLL) – a summary of important data from individual case summary reports. Essential information from each reported case is summarised in individual rows per case across the report sheet. For example individual case line listings includes date when report was received and seriousness of event.

Individual Case Safety Reports (ICSRs) - spontaneous adverse drug reactions reports or reports from non-interventional clinical trials. An adverse drug reaction report for

individual patients. Refers to the format and content for reporting suspected adverse drug reactions following administration of a medicinal product.[4]

MedDRA preferred term – term used to identify medical words eg. adverse drug reactions, symptom, sign, disease, diagnosis, therapeutic indication, investigation, surgical, or medical procedure, and medical, social, or family history characteristic.[5]

Medical Dictionary for Regulatory Activities (MedDRA) - standardised medical terminology used to facilitate the sharing of regulatory information for medical products which are intended for human consumption.[2]

Pharmacovigilance Query Library - consists of a number of options used for the evaluation of safety information, for signal detection, validation and assessments during other pharmacovigilance procedures.

Signal - Information on a new or known adverse event that is potentially caused by a medicine and that warrants further investigation. Signals are generated from several sources such as spontaneous reports, clinical studies and scientific literature.[6]

Signal Generation – a process which is used to identify a new adverse drug reactions or a change in the frequency of ADRs for medication.[6]

Signals of Disproportionate Reporting (SDR) - statistical associations between medicinal products and adverse events i.e. drug-event pairs identified by data mining algorithms using disproportionality analyses. The presence of this statistical association

does not imply any kind of causal relationship between the administration of the medicinal product and the occurrence of the reaction.[1]

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[1] Guideline on the use of statistical signal detection methods in the eudravigilance data analysis system. [Online]. European Medicines Agency: 2008. [cited 2018 Mar 1]. Available from: http://www.ema.europa. eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/11/WC500011434.pdf

[2] Eudravigilance system overview. [Online]. European Medicines Agency: 2018. [cited 2018 Mar 1]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000166 .jsp

[3] Eudravigilance access policy for medicines for human use. [Online]. European Medicines Agency: 2011. [cited 2018 Mar 1]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/07/ WC500108538.pdf

[4] Guideline on good pharmacovigilance practices (GVP). [Online]. European Medicines Agency: 2014. [cited 2018 May 29]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline /2014/09/WC500172402.pdf

[5] MedDRA Hierarchy. [online]. Medical Dictionary for Regulatory Activities.[cited 2018 Mar 1]. Available from: https://www.meddra.org/how-to-use/basics/hierarchy

[6] Signal Detection. [Online]. Drug Safety Research Unit: 2018. [cited 2018 Mar 1]. Available from: http:// www.dsru.org /consulting-on-risk-management/signal-detection/

List of abbreviations

ABI	Ankle Brachial Index
ACC	America College of Cardiology
ACCF	American College of Cardiology Foundation
ACS	Acute Coronary Syndrome
ADR	Adverse Drug Reaction
AF	Atrial Fibrillation
AHA	American Heart Association
ARISTOTLE	Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation
ATLAS ACS 2 - TIMI 51	Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects With Acute Coronary Syndrome 2–Thrombolysis In Myocardial Infarction 51
AVERROES	Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment
CAD	Coronary Artery Disease
CNS	Central Nervous System
COMPASS	Rivaroxaban for the Prevention of Major Cardiovascular Events in Coronary or Peripheral Artery Disease
CV	Cardiovascular
CVA	Cerebrovascular Accident
DVT	Deep Vein Thrombosis
EEA	European Economic Area
EMA	European Medicines Agency
eMC	Electronic Medicines Compendium
ENGAGE AF-TIMI 48	Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48
ePAD	Edoxaban in Peripheral Artery Disease
ESC	European Society of Cardiology
EU	European Union

EVDAS	Eudravigilance Data Analysis System
EVPM ICSRs	EudraVigilance Postauthorisation Module Individual Case Safety Reports
EVPM	EudraVigilance Post-authorisation Module
FDA	Food and Drug Administration
GI	Gastrointestinal
IC	Intermittent Claudication
ICLL	Individual Case Line Listing
ICSRs	Individual Case Summary Reports
IHD	Ischaemic Heart Disease
MACE	Major Adverse Cardiovascular Events
MALE	Major Adverse Limb Events
MDH	Mater Dei Hospital
MedRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
NOACs	Novel Oral Anticoagulants
PAD	Peripheral Arterial Disease
PAR-1	Protease-Activated Receptor-1
PE	Pulmonary Embolism
POPADAD	Prevention of Progression of Arterial Disease and Diabetes
PREFER-AF	Prevention of Thromboembolic Events – European Registry in Atrial Fibrillation
PV	Pharmacovigilance
RE-LY	Randomized Evaluation of Long-Term Anticoagulation Therapy
ROCKET-AF	Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation
SPC	Summary of Product Characteristics
THR	Total Hip Replacement
TIA	Transient Ischaemic Attack
TKR	Total Knee Replacement
UREC	University Research and Ethics Committee

VKAs	Vitamin K Antagonists
VOYAGER-PAD	Vascular Outcomes Study of Acetylsalicylic acid along with Rivaroxaban in Endovascular or Surgical Limb Revascularization for Peripheral Artery Disease
VTE	Venous Thromboembolism
WAVE	Warfarin Antiplatelet Vascular Evaluation
WHO	World Health Organisation

Chapter 1

Introduction

1.1 Adverse Drug Reactions

Medication administered with the aim of producing a therapeutic effect, may cause an unwanted adverse drug reaction (ADR) (Edwards and Aronson, 2000). In Europe, it is estimated that ADRs result in 197,000 deaths each year and contribute to about 5% of all hospital admissions (Bouvy, 2015). ADRs represent a considerable burden to society as ADRs can lead to morbidity, mortality and incur additional healthcare costs (Edwards and Aronson, 2000; Parameswaran et al, 2016). ADRs may be mistaken for a new medical problem or a complication of an existing diagnosis (Petrovic et al, 2012).

Classifications of ADRs have been created to help distinguish between types of ADRs. ADRs can be divided into Type A, Type B, Type C, Type D and Type E reactions (Pirmohamed et al, 1998; Cox, 2008; Greener, 2014; Kaufman, 2016; Patton and Borshoff, 2018). Table 1.1 shows the classification of ADRs.

Table 1.1: Classification of adverse drug reactions (Adapted from Patton K, Borshoff DC. Adverse drug reactions. Anaesthesia. 2018;73 (Suppl 1):76-84)

Classification of Adverse Drug Reactions	Definition
Type A	An exaggerated response of the medication, when administered at the recommended dose. Dose-dependent and predictable.
Type B	Idiosyncratic. Unusual responses to the medication which cannot be anticipated from the pharmacological properties of the medication. Dose-independent and unpredictable.
Type C	Occur over a continuous period of time
Type D	Delayed ADRs which occur sometime after the administration of the drug
Type E	Occur after the medication is withdrawn

The high numbers of deaths following ADRs and hospital admissions resulted in the development of an important reform of the European regulator system for pharmacovigilance (PV), which was put in place in July 2012. The aim of the reform for post-marketing surveillance of medicinal products, was to ameliorate public health in European countries by decreasing the considerable burden of disease associated to ADRs. Improving the monitoring of drugs during the post-marketing phase helps to better manage ADRs (Bouvy, 2015).

When the cause of an ADR is easy to identify, a risk-benefit decision on how to manage the ADR is required. A risk-benefit assessment helps to evaluate the severity of the reaction, asseses whether further treatment is necessary, and evaluates if the drug causing the ADR is indispensable to the patient. If more than one drug could be causing the ADR, the least important medications should be withdrawn first, preferentially one at a time. When the ADR is dose-related, a decrease in dose should be considered (Edwards and Aronson, 2000).

In a study by Pedros et al, results showed that more than 4% of urgent hospitalisations are due to ADRs, are dose-related and predictable in more than 90% of cases. The risk of hospitalisation was greater with increasing age and the amount of medication the patients were taking (Pedros et al, 2014). With increasing age, the risk of ADRs is higher due to alteration in drug's pharmacokinetics and pharmacodynamic of patients (Davies et al, 2007). A study by Wu et al, showed that in patients above 66 years of age, the odds of having severe ADRs is increased by 3% per year of increasing age (Wu et al, 2012).

A review of observational studies by Bouvy et al, demonstrated that there are limited studies which analysed ADRs in the outpatient setting, resulting in a scarcity of data with regards to the epidemiology of ADRs occurring in an out-patients scenario. The review considered all the epidemiological studies quantifying ADRs in Europe which were published over a 14 year period from 2000 to 2014. Results from the study showed that about 3.6% of hospital admissions were due to ADRs and that approximately 10% of admitted patients to European hospitals, experience an ADR when hospitalised (Bouvy et al, 2015).

1.2 Pharmacovigilance

The concept of pharmacovigilance (PV) encompasses the monitoring of ADRs. PV has been defined by the World Health Organisation (WHO) as 'the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.' Recognising and reporting of suspected ADRs through PV is important for patient safety especially for novel medications (Barry et al, 2014). PV promotes the safe and effective use of medications by providing adequate data for analyses of the risk-benefit profile of medications and may help in decreasing the risks. PV is an essential element of medicines regulation (Santoro et al, 2017).

The scope of PV is to capture, analyse, record, validate and perform systematic evaluation of ADRs which may occur following the administration of a particular drug. The objectives of drug monitoring include; identifying severe and unexpected ADRs, recognising rare or delayed ADRs, determining the frequency and seriousness of an ADR,

analysing the mechanisms involved and consequences which may occur and determining measures required to ensure safety of patients (Bucurescu, 2014).

Data from PV studies is beneficial for clinical practice as such data helps to generate new information about medication. New data can lead to, the withdrawal of drugs from the medical practice when a particular medication is not adequate for human consumption, or to a change in the drug prescription status. New therapeutic indications, contraindications and drug interactions can be identified and included to the medication profile (Bucurescu, 2014).

Monitoring of ADRs through PV is essential for new medications as evaluation of a drug's safety profile before release on the market for public consumption is limited. When a medicinal product is approved for use in the clinical setting, data with regards to the product is obtained from clinical trials. Controlled trials provide evidence on the drug's efficacy and are not usually designed to detect ADRs (Barry et al, 2014). Trials show the benefit-risk profile of the medication under strictly monitored conditions. Additional data on the benefit-risk profile of the drug can be further observed following reported ADRs (Santoro et al, 2017). Rare ADRs are not always identified in clinical trials and the use of the medication in real world scenarios may give rise to new data about ADRs (Barry et al, 2014). PV assures that the safety of medicinal products which are utilised by the population is under ongoing review (Santoro et al, 2017).

PV has expanded into a quality system-based scientific discipline and incorporates a number of activities that are useful for the monitoring of medicines available on the

market (Santoro et al, 2017). When assessing a suspected ADR, it is necessary to adopt a systematic approach which involves a standardised clinical tool such as the Naranjo Probability Scale or by using other causality assessment methods (Naidu, 2013; Barry et al, 2014). The Naranjo Probability Scale and causality assessment methods are used to determine if there is any association between the exposure of a drug and the occurrence of an ADR. Some healthcare professionals are still not aware of the ADR reporting process or the usefulness of causality assessment methods (Naidu, 2013).

The majority of reported ADRs comes from spontaneous reporting done by healthcare professionals usually on a voluntary basis (Hazell and Shakir, 2006). Reported ADRs can be accessed from PV databases and data evaluated for potential ADRs safety signals (Monaco et al, 2017). The main purpose of spontaneous ADR reporting is to give alerts of possible harmful ADRs which have not been identified before the drug was available on the market. ADRs may be difficult to identify due to limitations encountered during clinical trials such as small sample size, duration of the trial and extrapolation of data (Evans et al, 2001).

Limited information about ADRs is available when medications receive marketing authorisation and to ensure safety for patients, it is necessary for regulatory authorities to gain post-marketing information about potential ADRs (Lasser et al, 2002). Spontaneously reported ADRs give additional information from real-life scenarios which may be used in safety-related studies. Spontaneous reporting of ADRs is the key element of PV. Data about consumption of medication is rarely used when analyses of ADRs are performed (Svendsen et al, 2018).

1.2.1 Eudravigilance

Eudravigilance is the European data processing system for managing and evaluating data on reported suspected ADRs of medicines which have been authorised in the European Economic Area (EEA). The European Medicines Agency (EMA) manages the system on behalf of the European Union (EU) medicines regulatory network.[1] The EMA is responsible for the evolution, maintenance and coordination of Eudravigilance. Reports submitted to Eudravigilance include ADRs of medications reported during the pre- and post-marketing phases.[2] Eudravigilance started its operation in December 2001 (Postigo et al, 2018).

Eudravigilance helps to monitor the safety of medicines, facilitates the electronic reporting of suspected ADRs associated with administration of medication, and effectively evaluates information. Monitoring of ADRs is important in the early detection of potential safety concerns related to medicine. Eudravigilance ensures the safe and effective use of medication by assisting in the electronic exchange of individual case safety reports (ICSR) and by aiding in the early detection and analysis of potential safety signals. Eudravigilance ensures that the optimal product information for medicines is available.[3] The Pharmacovigilance Risk Assessment Committee is the main entity which

[1] Eudravigilance [Online]. European Medicines Agency: 2018. [cited 2018 Feb 22]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000679.jsp&mid=WC0b01ac05800250b5

[2] EudraVigilance – European database of suspected adverse drug reaction reports. [Online]. European Medicines Agency: 2018. [cited 2018 May 25]. Available from: http://www.adrreports.eu/en/eudra vigilance .html

[3] Screening for adverse drug reactions in Eudravigilance. [Online]. European Medicines Agency: 2016. [cited 2018 Feb 22]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/12/WC500218606.pdf

is responsible for assessing and monitoring safety of the medicinal products in the EU (Santoro et al, 2017). The collection of ICSRs about suspected ADRs in individuals exposed to the medication provides data which helps to detect ADRs[4].

Assessment of safety information from spontaneous reporting systems, following introducion of medication on the market and use in clinical scenarios, has been shown to be valuable for detecting and analysing risks associated with medications. Eudravigilance facilitates effective safety monitoring of authorised drugs, provides access to data for research and provides information on suspected ADRs to healthcare professionals and patients. The electronic reporting of suspected ADRs, from use of medication during clinical trails or in medical practice, became mandatory in the EEA in November 2005 (Postigo et al, 2018).

In Eudravigilance, statistical methods are used to evaluate ADRs data and to determine if there are any potential safety issues related to a particular drug. Eudravigilance uses a method to measure disproportionality of reporting of drug-event pairs which are referred to as Signals of Disproportionate Reporting (SDR) and provides information based on disproportionate measures of reported ADRs. Statistical calculations are used to determine signal generation based on the proportionate approach and stability of the database. The method involves the calculation of the proportions of specified ADRs or group of ADRs for medications of concern, where the comparison is done with all the other medications found in the database (Evans et al, 2001).

[4] Screening for adverse drug reactions in Eudravigilance. [Online]. European Medicines Agency: 2016. [cited 2018 Feb 22]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/12/WC500218606.pdf

Eudravigilance receives reports of suspected ADRs during the pre- and post-authorisation phases of medication. The system permits the detection of signals of suspected ADRs which were not associated with a particular drug and of new information related to known ADRs. Data submitted to Eudravigilance is evaluated regularly and where needed regulatory action may be recommended.[5] The procedure of examining data from spontaneous ADR reporting is known as signal generation (Evans et al, 2001).

1.3 Thromboembolic disease

Thromboembolic conditions cause considerable burden to patients and have been attributed to one in four deaths worldwide in 2010 (Lozano et al, 2012). Thromboembolic diseases consist of arterial disease and venous disease (Wendelboe and Raskob, 2016). Thromboembolic arterial disease can lead to acute myocardial infarction (MI), atherothrombotic stroke and peripheral artery disease (PAD), while venous thromboembolism (VTE) can lead to deep vein thrombosis (DVT) and pulmonary embolism (PE) (Agnelli and Becattini, 2006).

During homeostasis there is a balance between procoagulant, anticoagulant and fibrinolytic entities. Adequate flow of blood through vessels results from an equilibrium between haemostasis and fibrinolysis. Several factors can upset the balance, leading to the pathologic formation of a thrombus in blood vessels. Thrombi can obstruct the flow

[5] Eudravigilance [Online]. European Medicines Agency: 2018. [cited 2018 Feb 22]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000679.jsp&mid=WC0b01ac05800250b5

of blood, or detach and move to another vessel (Spronk et al, 2014). Certain pathological conditions lead to the intravascular formation of blood clots which cause the activation of the coagulation cascade and platelets, leading to the formation of an occlusive clot which may result in cardiovascular (CV) events (Lüscher and Steffel, 2016). Platelets are crucial in the initiation, evolution and thrombotic complications associated with atherosclerosis (Massberg et al, 2002; Huo et al, 2003).

A link could be present between venous and arterial thrombosis as both diseases share some similarities. Arterial and venous disease can be seen as different manifestations of the same condition (Agnelli and Becattini, 2006). A study by Libertiny and Hands, showed a high prevalence of venous thrombosis in PAD patients which was related to the severity of ischaemia. Results demonstrated that a reduced ankle branchial index (ABI) is an independent predictor of deep vein thrombosis (Libertiny and Hands, 1999). The lower the ABI, the greater the ischaemia, that is the greater is the resistance to arterial blood flow (Aronow, 2007). A low ABI value is suggestive of atherosclerosis in the legs. In clinical practice and epidemiological studies an ABI which is less or equal to 0.90 is usually taken as the cut-off point to determine the presence of PAD, both symptomatic and asymptomatic (Criqui and Aboyans, 2015). In another study, carried out to assess the relation between atherothrombotic disease and venous thromboembolism, results showed an increase in the risk of VTE in patients with arterial thrombosis ($p < 0.001$), particularly in patients with cervico-cranial and peripheral artery thrombosis (Eliasson et al, 2006). A study by Prandoni et al concluded that patients with idiopathic VTE, have a 60% higher risk of developing symptomatic atherosclerotic disease compared to patients with secondary venous thrombosis (Prandoni et al, 2006).

The studies by Libertiny and Hands, Eliasson et al and Prandoni et al discuss the connection that possibly exists between arterial and venous thrombosis. Evidence shows a possible connection between arterial and venous thrombosis (Agnelli and Becattini, 2006).

1.3.1 Antithrombotic therapy and thromboprophylaxis

Antithrombotic medications such as aspirin and warfarin were the only options for thromboprophylaxis for many years (Bista et al, 2014). Thromboprohylaxis has caused an increase in the need to identify antithrombotic medications which are effective and have a good safety profile. Antiplatelets and anticoagulants are two classes of medications used for thromboprophylaxis. Antiplatelets are indicated for the prevention of arterial thromboembolism (Alban, 2008). Anticoagulants are indicated for the prevention and treatment of both venous and arterial thromboembolic disease (Linkins and Weitz, 2005; Alban, 2008). Antithrombotic medication is used in treating and preventing a number of vascular complications (Mega and Simon, 2015). Thromboprophylaxis is used in different settings such as in surgical patients with a risk of DVT including high risk orthopaedic patients, patients at risk of VTE such as deep vein thrombosis (DVT), patients with PAD and cardiac disease (O'Donnell and Weitz 2003; Linkins and Weitz, 2005; Rooke et al, 2011; Eikelboom et al, 2012; Rajabi et al, 2012).

Haemostasis involves an intricate interaction between the vascular endothelium, platelets and coagulation factors. An inbalance can lead to the formation of clots in arteries or veins which manifest as vascular complications such as venous thromboembolism or

acute coronary syndrome (ACS) (Mega and Simon, 2015). Effective antithrombotic medication for managing thromboembolic disease is necessary. In haemostasis, a balance between the deposition and removal of fibrin is important. Haemostasis protects the vascular system from blood loss at the site of injury and helps in maintaining blood fluidity. The target of using antithrombotic medication is to optimise the balance between efficacy, that is, avoiding the disruption in the equilibrium of haemostasis, and safety, that is avoiding the risk of ADRs such as bleeding (Dahl, 2012). Blood coagulation is a complex mechanism involving various processes (Monroe and Hoffman, 2006).

Plaque rupture and subsequent thrombosis activates platelets and coagulation factors. Platelets are the main components involved in the formation of atheromatous plaques and are elevated after an acute atherothombotic event involving plaque rupture. Pathogenesis of atherothrombosis involves activation of clotting factors and generation of thrombin which is associated with platelet activation and fibrin formation (Jacomella et al, 2013). Platelet aggregation can trigger thrombus formation particularly during conditions which increase the risk of a thrombotic event (Mega and Simon, 2015).

Anticoagulant and antiplatelet medications have been used and studied in a number of trials for both primary and secondary prevention of atherothrombosis (Jacomella et al, 2013). Antiplatelet agents and anticoagulants have complementary mechanisms of actions and there is growing evidence which supports that the clotting factor thrombin is involved in recurrent ischaemic events in patients who have ACS (Yeh et al, 2015).

The ideal antithrombotic agent should be effective for its intended use and with a low risk of ADRs. Antithrombotic medication should be effective in preventing thromboembolic events and cause minimal ADRs such as bleeding to patients (Ramos-Esquivel, 2015). New information on the pharmacology of antithrombotic medication and the mechanisms involved in thrombosis, has contributed to the development of novel agents with a faster onset of action, less drug-drug interactions and less interpatient variability when compared to conventional therapy such as warfarin (Mega and Simon, 2015). The introduction of newer agents into clinical practice such as the novel oral anticoagulants (NOACs) has provided alternatives for thromboprophlaxis (Bista el al, 2014).

1.4 Aspirin and its indications

The use of aspirin dates back to the late 1890s and has been used as an anti-inflammatory, analgesic and antipyretic agent (Vane and Botting, 2003). Aspirin is the most commonly used antiplatelet agent worldwide (Berger et al, 2009) and inhibits platelet activity by irreversibly inhibiting cyclooxygenase activity (Mekaj et al, 2015). Aspirin is indicated for the primary and secondary prevention of atherothrombotic vascular events (Gaglia and Clavijo, 2013). Aspirin is used for the prevention of arterial thombotic events and prevention of VTE especially for recurrent VTE (Mekaj et al, 2015). Aspirin is indicated for treatment of CV disease such ACS and PAD (Eikelboom et al, 2012; Ugurlucan et al, 2012). Aspirin is used in patients following an acute MI, in the secondary prevention of cerebrovascular accidents (CVA), in individuals following a transient ischaemic attack (TIA) or recurrent CVA and in patients with an acute ischaemic stroke (ISIS-2 Collaborative Group, 1988; SALT collaborative Group, 1991; Lindblad et al, 1993;

CAST Collaborative Group, 1997; Eikelboom et al, 2012). Aspirin decreases the risk of MI and deaths in patients with stable and unstable angina (RISC group, 1990; Juul-Möller et al, 1992). Low dose aspirin is indicated in patients recovering from surgeries (Mekaj et al, 2015). Apart from prevention of atherothrombotic events, aspirin at a higher dose is indicated for analgesia (Ugurlucan et al, 2012).

Aspirin reduces the risk of thrombosis and ischaemic events by inhibiting thromboxane A2 activation pathway (Angiolillo and Ferreiro, 2013). Thromboxane has a role in the aggregation of platelets that leads to the formation of blood clots. Platelets are involved in the pathogenesis of atherosclerosis and atherothrombotic events including CVA and MI. When plaque rupture occurs, platelets adhere to the site of injury, aggregate and become activated and can potentially lead to vascular occlusions. Aspirin works by preventing platelet aggregation (Reinhart, 2013).

Patients on aspirin have a risk of having ischaemic events, as platelet activation continues via other pathways independent of thromboxane A2, mainly the protease-activated receptor-1 (PAR-1) platelet activation pathway which is stimulated by thrombin (Angiolillo and Ferreiro, 2013). PAR-1 activation by thrombin is one of the most potent activation pathways which can result in the formation of a thrombus (Brummel et al, 2002; Mann, 2003). Thrombin is the most potent platelet agonist (Direct Thrombin Inhibitor Trialists' Collaborative Group, 2002).

1.5 Novel oral anticoagulants and their indications

The risks related to thromboembolic diseases and limitations associated with antithrombotic medications led to the development of the NOACs. The NOACs work by directly inhibiting a single enzyme in the coagulation cascade; factor Xa or thrombin (factor IIa) (Weitz et al, 2008). To date there are five NOACs which have been approved for use. Dabigatran and rivaroxaban were developed in 2008, followed by apixaban in 2011. Edoxoban was developed in 2015 (Weitz and Harenberg, 2017). Dabigatran was the first approved NOAC for use in 2010 by the Food and Drug Administration (FDA). Rivaroxaban was the second NOAC to be approved in 2011, while apixaban was approved in 2012 and edoxaban in 2015. The latest approved NOAC was betrixaban in 2017 (Rose and Bar, 2018). Apixaban, edoxaban and rivaroxaban are factor Xa inhibitors, while dabigatran is a thrombin inhibitor. Approved indications for rivaroxaban, dabigatran and apixaban include stroke prevention in atrial fibrillation (AF), treatment of VTE including DVT and PE and thromboprophylaxis following hip or knee arthroplasty (Yeh et al, 2015; Chan et al, 2016). Betrixaban inhibits free factor Xa and prothrombinase activity and causes a decrease in thrombin production. Betrixaban does not directly affect platelet aggregation and is approved for hospitalised acutely medically ill patients requiring long-term venous thromboembolism prophylaxis and who are at risk of thromboembolic complications (Rose and Bar, 2018).

Factor Xa and thrombin are components of the coagulation cascade and other biological and pathophysiological pathways. They are recognised targets for effective anticoagulation treatment (Eriksson et al, 2011). The endothelium, platelets, pro-

inflammatory cytokines, chemokines and serine proteases such as factor Xa and thrombin, via the activation of PAR are crucial for the promotion of inflammation and leukocyte migration which causes the start of atherosclerosis (Esmon, 2014; Spronk et al, 2014). Factor Xa is responsible for starting the final common pathway of the coagulation cascade leading to the formation of thrombin which activates other coagulation related reactions and promotes platelet activation (Mega el al, 2012). Factor Xa and thrombin have an essential role in mediating cellular signalling effects related to the initial phase of atherosclerosis development. The effect of factor Xa and thrombin is associated with hypercoagulability and thrombotic changes (Spronk et al, 2014). Targeting factor Xa, blocks the formation of thrombin and reduces the propagation of a thrombus (Cavender et al, 2015). Inhibition of factor Xa decreases the generation of thrombin leading to a reduction in platelet activation (Bauersachs et al, 2010). Evidence shows that direct thrombin inhibitors hinder the formation and size of atherosclerotic plaques and impede the progression of endothelial injury-associated stenosis in an apolipoprotein E-deficient mouse model (Lee et al, 2012; Borissoff et al, 2013).

The clotting factors, factor Xa and thrombin are responsible for causing coagulation and inflammation (Ten Cate, 2012; Jacomella et al, 2013). Anti-FXa inhibitors and direct thrombin inhibitors target the pathway which is responsible for thrombin generation with the potential of preventing thrombosis or atherosclerosis (Jacomella et al, 2013).

Thrombin has an important role in blood coagulation and thrombus formation. Thrombin converts fibrinogen to fibrin and propagates its own generation by feedback activation of factors V, VIII and XI (Direct Thrombin Inhibitor Trialists' Collaborative Group, 2002).

Thrombin activates platelet PARs which mediate platelet aggregation. Thrombin is involved in the final step of blood coagulation (Bauer, 2006). Studies have demonstrated that coagulation proteins, such as factor Xa and thrombin, have an effect on coagulation, anti-inflammation processes and can potentially affect the progression of conditions such as atherothrombosis (Ellinghaus et al, 2011; Eriksson et al, 2011; Zhou et al, 2011; Borissoff et al, 2013).

The development of NOACs contributed to new options for the management of thromboembolic events (Esmon, 2014). There is evidence that shows that factor Xa and thrombin are involved in anti-inflammatory activities and atherosclerotic plaque stabilisation processes (Joo et al, 2009). In atherosclerosis, a relationship between coagulation and inflammation has been identified (Borisoff et al, 2011).

A study by Cohen et al, was conducted to compare the safety and efficacy of apixaban, dabigatran and rivaroxaban in the extended treatment and prevention of VTE. Results showed that the three NOACs are effective in preventing VTE or VTE-related death. The risk of composite efficacy outcome (VTE or VTE-related death) was statistically significantly lower with NOACs when compared to aspirin. The risk of composite efficacy outcome was not statistically significantly different between the NOACs. Bleeding risk differed between different NOACs, with apixaban showing the most favourable profile when compared to the other NOACs and aspirin (Cohen et al, 2016). In another study by Tereschckenko et al, the aim was to compare the safety and efficacy of antiembolic interventions (apixaban, dabigatran, edoxaban, rivaroxaban, VKA, aspirin and Watchman device) in nonvalvular AF. Results showed that all antiembolic

interventions have measurable, but not equivalent safety and efficacy. All antiembolic interventions significantly decreased all-cause mortality and risk of stroke or systemic embolism in nonvalular AF individuals. Results demonstrated an overlap in the efficacy and safety of individual treatments. Significant differences in primary efficacy and safety outcomes were observed between individual NOACs. The study concluded that from all the interventions, the four NOACs and the Watchman device are probably the most effective, life-saving antiembolic interventions (Tereschcheno et al, 2016).

The introduction of NOACs in the medical field resulted in an advancement in managing anticoagulation. The properties of NOACs helped to overcome the limitations of the widely used anticoagulant warfarin (Yeh et al, 2015). The introduction of NOACs provided another option of antithrombotic medication instead of the vitamin K antagonists (VKAs). When compared to oral VKAs, direct thrombin inhibitors and factor Xa inhibitors show an overall favourable pharmacological properties (Jacomella et al, 2013). In phase 3 clinical trials, which included more than 100 000 patients, NOACs have shown to be at least as effective as VKAs. The NOACs are considered to have a better safety profile than VKAs and are associated with less bleeding risks, particularly a decrease in the risk of intracranial bleeding (Chai-Adisaksopha et al, 2014;Yeh et al, 2015). NOACs can be given in fixed doses with no need of routine coagulation monitoring. As opposed to warfarin, the action of NOACs is directed at a single clotting enzyme. Dabigratan inhibits thrombin while rivaroxaban, apixaban and edoxaban inhibit factor Xa. The onset of action of NOACs is rapid and peak plasma concentrations are obtained 1 to 4 hours after oral administration and have a half-life of approximately 12 hours (Yeh et al, 2015). NOACs have a rapid offset of action, predictable pharmacodynamics, a wide therapeutic window which limits monitoring needs. NOACs

have a short half-life which simplifies the use of these agents in individuals requiring surgical procedures, likely eliminating the need for bridging therapy (Connolly and Spyropoulos, 2013).

Data on the use of NOACs in the clinical scenario and data on whether NOACs are used for the approved indications is limited. A study by Desai et al, 2014, was carried out to identify patients with nonvalvular AF who were prescribed an oral anticoagulant between 2010 and 2013. The study observed that there was a significant decrease in the proportion of individuals with AF who were started on warfarin. Results showed that by June 2013, 62% of patients requiring an oral anticoagulant were started on either dabigatran, rivaroxaban or apixaban and that 98% of new anticoagulation expenses for patients started on anticoagulation therapy, were due to the use of NOACs. (Desai et al, 2014).

Post-marketing studies demonstrate favourable results for NOACs when used in the clinical scenario. Ongoing studies are analysing the use of NOACs for new indications such as heart failure, CAD, PAD, antiphospholipid syndrome, cancer and prevention of thrombosis in patients with embolic stroke of unknown source (Chan et al, 2016).

1.5.1 Adverse drug reactions and novel oral anticoagulants

Major bleeding is a serious ADR which is related to the use of NOACs. Non-major bleeding is associated with NOACs, but does not result to a need for a change in dose, interruption of the medication or hospitalisation (Prisco et al, 2017). The relatively short

half-life of NOACs and the reversible inhibition of factor Xa and thrombin by NOACs, shortens the duration of increased risk of bleeding (Harder and Graff, 2013). Other ADRs include gastrointestinal, haematological, CV and neurological and skin reactions (Prisco et al, 2017). Results from studies showed NOACs to have a promising safety profile with respect to bleeding (Connolly et al, 2009; Granger et al, 2011; Patel et al, 2011).

To date there are unanswered safety issues related to NOACs which need to be analysed and available postmarketing information on the risks associated with NOACs is conflicting (Monaco et al, 2017). In a meta-analysis of randomised trials of patients receiving NOACs or warfarin, results showed that NOACs are significantly associated with less intracranial bleeding and mortality. Risk of major bleeding for NOACs was found to be comparable to warfarin but risk of gastrointestinal bleeding was greater than that of warfarin (Ruff et al, 2014). Results from another study showed that, neither rivaroxaban nor dabigatran were associated with a statistical increase in the risk of gastrointestinal bleeding compared to warfarin (Chang et al, 2015) In a meta-analysis by Rong et al, conclusions showed that NOACs are associated with a lower risk of major bleeding events compared to warfarin (Rong et al, 2015).

There is a controversy on whether NOACs increase the risk of hepatoxicity. Liver injury related to the administration of NOACs has been reported in some patients as described in case reports and clinical studies (Liakoni et al 2015). Conclusions from a meta-analysis show that NOACs do not increase the risk of drug-induced liver injury (Caldeira et al, 2014).

1.5.2 Trials on novel oral anticoagulants

The NOACs are being investigated for new indications. The favourable safety profile and advantages of NOACs when compared to VKAs has resulted in further investigations on the use of NOACs for novel indications (Weitz and Harenberg, 2017). NOACs have shown to be at least as effective as VKAs and have been associated with less serious bleeding (Ruff et al, 2014; Van der Hull et al, 2014).

In the Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects With Acute Coronary Syndrome 2–Thrombolysis In Myocardial Infarction 51 (ATLAS ACS 2-TIMI 51) study a total of 15,526 patients with a recent ACS were assigned to three arms: patients receiving 2.5mg rivaroxaban twice a day, patients receiving 5mg of rivaroxaban twice a day and patients receiving placebo. The primary efficacy end point was that of composite death from CV events, MI and CVA. Results from the study showed that there was a significant reduction in the primary efficacy end point in both groups receiving rivaroxaban with rates of 8.9% and 10.7% respectively, when compared to patients receiving the placebo. Results from the study showed that rivaroxaban enhanced the risk of major bleeding and intracranial haemorrhage but did not increase the risk of any fatal bleeding (Mega et al, 2012).

Another study was conducted to determine the incidence, type and size of MIs of patients recruited in ATLAS ACS 2-TIMI 51. Results from the study demonstrated that rivaroxaban significantly decreased the incidence of spontaneous MI particularly MIs with extensive biomarker release and ST-segment elevation (Cavender et al, 2015).

A meta-analysis by Ruff et al, was carried out to compare the risk-benefit profile of the four NOACs apixaban, dabigatran, edoxaban and rivaroxaban using four randomised controlled trials; Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY), Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF), Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) and Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48). Results from the meta-analysis showed that NOACs have a positive risk-benefit profile, significantly decreased CVA, intracranial haemorrhage and death when compared to warfarin and have a comparable risk of major bleeding as warfarin (Ruff et al, 2014).

In the Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) trial, apixaban was compared to aspirin in patients with AF who had an increase in stroke. Results from the study showed that apixaban was superior to aspirin for preventing stroke or systemic embolism. Both apixaban and aspirin had comparable rates of major bleeding and intracranial bleeding (Connolly et al, 2011).

The aim of the Prevention of Thromboembolic Events – European Registry in Atrial Fibrillation (PREFER-AF) is to analyse the efficacy of NOAC medication in the prevention of endothelial dysfunction and the progression of atherosclerosis in patients with atrial AF. Patients participating in the study will be assigned to the dabigatran group

(110mg or 150mg twice daily), the rivaroxaban group (20mg daily) and warfarin group (control group). The study is ongoing. (Kim et al, 2016).

1.6 Peripheral Artery Disease

PAD occurs when there is partial or complete blockage of one or more arteries found in the peripheries (Hiatt et al, 2008). PAD is a systematic manifestation of atherosclerosis (Creager et al, 2012). Atherosclerosis is the main cause of PAD and the occurrence of PAD shows the presence of a generalised atherosclerotic burden (Criqui, 2001; Fowkes, 2001; Diehm et al, 2004). Atherosclerosis in arteries found in the peripheries is chronic and develops gradually causing narrowing of arteries. The degree of narrowing effects clinical presentations which vary from intermittent claudication (IC), exercise limitations, ischemic pain, ulceration at the lower extremities and gangrene of the toes. PAD patients may have acute events associated with thrombosis, embolism and major arterial occlusion (Singh et al, 2017).

There are more than 200 million individuals worldwide who suffer from PAD (Fowkes et al, 2008). PAD has a prevalence of approximately twenty percent in people who are older than sixty years of age (Sigvant et al, 2016). Patients with PAD have platelet hyperactivity and an increased risk of thromboembolic events and death (Hackam and Eikelboom, 2007; Kotschy et al, 2015). PAD patients have a threefold increase in risk of having major adverse cardiovascular events (MACE) including MI and stroke, and death when compared to patients without PAD (Robless et al, 2003; Jacomella et al, 2013). Patients with PAD have a greater risk for an acute CV event such as aortic aneurysm

rupture, ischemic ulceration, amputation and vascular death (Newman et al 1997; Newman et al, 1999). When managing PAD the aim is to decrease the risk of CV events, enhance walking distance and functional status in people with IC and decrease amputation risk in critical limb ischemic patients (Schmit et al, 2014).

The prevalence of individuals with PAD is increasing and even though medication which can minimise CV risk and prevents progression of disease is available, some patients are undiagnosed or not adequately treated (Cooke and Wilson, 2010; Paraskevas et al, 2013; Olin et al, 2016). Medications indicated for preventing vascular events include antiplatelet agents, statins and angiotension converting enzyme inhibitors (Hirsch et al, 2001). PAD can lead to generalised vascular atherosclerosis. Patients with PAD have a greater tendency to have other arterial diseases including carotid or CAD, cerebral and renal artery disease and abdominal aortic aneurysms (Criqui and Denenberg, 1998; Paraskevas et al, 2013). PAD leads to limb pain on exertion, decreases functional capacity and the quality of life (McDermott et al, 2004).

PAD can be symptomatic or asymptomatic. The greater risk of CV morbidity and mortality which is associated with PAD is also observed in patients who are asymptomatic (Criqui et al, 1992). Asymptomatic disease refers to patients who lack exertional leg symptoms (Hiatt et al, 2008). PAD patients have functional impairment because of changes in the calf muscle blood vessel supply, a decrease in leg strength and impaired metabolic function (McDermott, 2015). PAD patients have a risk of subsequent compromised ambulation, lower extremity ulcers and the need of vascular surgery or amputation (Golomb et al, 2006).

Platelets and clotting factors have a role in the progression of PAD and the propagation of complications (Hackman and Eikelboom, 2007), thus, antiplatelet and anticoagulant medications are elemental in preventing macrovascular complications in PAD patients (Poredos and Jezovnik, 2010). Patients with PAD have platelet hyperaggregability, elevated levels of soluble platelet activation markers, increased thrombin generation and a modified fibrinolytic ability. Markers which typify the pro-thrombotic environment for PAD give an indication of future CV events. An increase in markers correlates strongly with the severity of the condition and there is the need to consider antithrombotic prophylaxis in PAD patients (Hackman and Eikelboom, 2007).

In a study, by Hussein et al, which considered data from seven clinical studies, results showed that patients with concomitant CAD and PAD had more extensive and calcified coronary atherosclerosis, impaired arterial remodelling and accelerated disease progression. Findings from the study showed the need to consider risk-modifying strategies for patients who are diagnosed with PAD and who have an increased risk of CV events (Hussein et al, 2011).

Diagnosing and treating PAD in the early stages, that is asymptomatic stage, can potentially be of benefit with regards to interventions aimed at improving risk factors common to atherosclerotic diseases (Criqui and Aboyans, 2015) and in minimising atherosclerotic complications.

1.7 Antithrombotic therapy in peripheral artery disease

When managing PAD, treatment should not only be targeted to improve peripheral circulation, but a more dynamic approach aimed at reducing risk factors, decreasing morbidity and improving the quality of life should be considered. PAD can be managed by targeting risk factors which are related to the progression of generalised atherosclerotic burden, administering medication therapy and undergoing necessary interventions aimed at reducing symptoms (Ouriel, 2001). Two main targets necessary for treating PAD patients are to decrease the progression of lower limb atherosclerosis and to avoid future CV events (Foley et al, 2016).

Antiplatelet medications are indicated for the prevention of vascular events, but the role of oral anticoagulant medications in minimising CV complications is still uncertain (Warfarin Antiplatelet Vascular Evaluation Trial Investigators et al, 2007). To date aspirin is the mainstay therapy for the prevention of MACE in PAD, with clopigodrel as an alternative medication. Aspirin has been used in PAD patients, as has warfarin. Use of warfarin in PAD is limited (Whayne, 2012). In elderly patients with PAD, the incidence of CAD and CVAs can be as high as 68% and 42% respectively (Ness and Aronow, 1999). The relative risk of CV mortality in PAD patients is increased by almost 6-fold (Hirsch et al, 2006). A substantial number of patients with apparently stable PAD, have suffered a MI, CV attack or CV death within a year (Steg et al, 2007). There is the need to ameliorate secondary prevention strategies and improve patient's clinical outcome (Cappato and Welsh, 2016).

In a study by Sigvant et al, results showed that more than one in five patients who are diagnosed with PAD in a hospital scenario, will die within one year and that one in six patients will have a CV event within one year. The study also demonstrated that a number of patients diagnosed with PAD, did not receive medication for secondary prevention. The high mortality rate and risk of a vascular events show that the use of antithrombotic therapy is essential in managing patients with PAD as antithrombotic therapy helps decrease risks. Risk prevention should be adopted in PAD patients both by incorporating lifestyle changes and by introducing secondary prevention drug therapy (Sigvant et al, 2017).

A study by Rajagopalan et al, was carried out to assess the correlation between platelet activation and severity of PAD. Participants of the study consisted of PAD patients with IC or subcritical limb ischaemia. Results showed that platelet activation is significantly higher in patients with subcritical limb ischaemia compared to those with IC. Both patient groups were administered aspirin. Results showed that circulating platelets are more reactive in individuals with more severe PAD (Rajagopalan et al, 2007). Patients with a high amount of reactive platelets have a greater risk for thrombus formation (Rajagopalan et al, 2007) and thus additional therapy in high risk PAD patients should be considered.

The Warfarin Antiplatelet Vascular Evaluation (WAVE) trial compared PAD patients who were administered combination therapy with antiplatelet and an oral anticoagulant (warfarin) or an antiplatelet alone. Results from the WAVE trial showed that combining an oral anticoagulant to antiplatelet medication was not more effective than using antiplatelet therapy alone to limit MACE in patients with PAD. The combination regimen

was associated with an increase in life-threatening bleeding and other bleeding events (Warfarin Antiplatelet Vascular Evaluation Trial Investigators et al, 2007).

When choosing antithrombotic therapy, the regimen should be effective in lowering MACE complications and with a good safety profile such as having a low bleeding risk. When compared to warfarin, the NOACs have better efficacy and safety profile. The combination of two antithrombotic medication is still uncertain. Data on the use of NOACs in PAD is limited and further studies and analysis are necessary to establish if NOACs can be used for new indications while ensuring long term safety (Tsipis et al, 2014).

The use of antithrombotic medication in PAD patients is important as it aims to decrease the risk of serious CV events in PAD which is associated with a high degree of atherosclerotic burden (Hu and Jones, 2016). Guidelines suggest that symptomatic patients should be on an antithrombotic agent, specifically an antiplatelet medication (Rooke et al, 2011). In symptomatic PAD there is no general agreement on which antiplatelet medication should be used (Katsanos et al, 2015).

There is a scarcity of clinical data, clinical guidelines and randomised controlled studies in the PAD population (Singh et al, 2017). Studies which analysed the role of antiplatelet agents in PAD have given conflicting results (Hu and Jones, 2016). Aspirin is the primary agent used in patients with CV disease and concomitant PAD symptoms, even though literature lacks evidence on the use of aspirin in PAD (Berger et al, 2009; Berger et al, 2011). In individuals with PAD, there is an evident unmet need for therapy that is more

effective but with a comparable safety profile to aspirin (Cappato and Welsh, 2016). Further studies for the use of NOACs in new clinical settings and patient populations are needed.

1.7.1 Aspirin use in peripheral artery disease

Aspirin is indicated for secondary prevention in PAD patients (Whayne, 2012; Gerhard-Herman et al, 2016). Evidence supporting the use of aspirin for secondary prevention of vascular events in PAD is not conclusive (Berger et al, 2009). The optimal antiplatelet therapy and length of treatment for secondary prevention in PAD remains uncertain, because of the limited and conflicting data in the PAD patient cohort (Foley et al, 2016). Antiplatelet medication is indicated for the secondary prevention of macrovascular complications. Data shows a high rate of CV events in PAD patients (Antithrombotic Trialists' Collaboration, 2002). Aspirin is the recommended antiplatelet agent in PAD, with Class I Level of Recommendation A. Use of aspirin has not demonstrated to decrease CV events in the setting of PAD. (Berger and Hiatt, 2012).

The 2016 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines recommend the use of aspirin in the prevention of atherothrombotic events in PAD patients as a result of the benefit obtained in other vascular diseases when using aspirin (Alonso-Coello et al, 2012; Gerhard-Herman et al, 2017). The use of aspirin as monotherapy may not be sufficient in reducing MACE in patients with PAD. The guideline suggests the use of another antiplatelet agent in high risk PAD patients, while considering the risk of bleeding (Rooke et al, 2011).

Aspirin is the first line drug for secondary prevention in PAD. The use of aspirin does not seem to be effective in all PAD patients (Lee et al, 2005). Results from a meta-analysis analysing the efficacy of aspirin in patients with PAD showed that aspirin decreases the risk of non-fatal stroke but is ineffective for the prevention of all-cause or CV mortality (Berger et al, 2009). Aspirin decreases the risk of thrombotic events by approximately 25%, showing that more effective medication needs to be identified (Weitz and Harenberg, 2017). There is uncertainty on whether PAD patients are administered a low dose of aspirin or are not compliant to medication therapy. Patients may have different capabilities to absorb aspirin or may have underlying genetic factors that make aspirin ineffective (Lee et al, 2005). Patients who do not respond to aspirin, are defined as being aspirin 'resistant', meaning that efficacy of aspirin varies in different patients (Poredos and Jezovnik. 2010). Patients who do not respond effectively to aspirin are potential candidates who can be considered for alternative drug therapies.

In the Prevention of Progression of Arterial Disease and Diabetes (POPADAD) study, asymptomatic PAD patients with diabetes were administered aspirin at a dose of 100mg daily or a placebo. Results showed no evidence which supports aspirin use in the primary endpoint of CV death, MI, CVA or amputation due to ischemia (Belch et al, 2008). In another study, a meta-analysis involving eighteen trials with a total of 5269 patients, the use of aspirin in PAD patients was analysed versus a placebo. The meta-analysis showed a significant decrease in nonfatal stroke with no statistical significant reductions in nonfatal MI, CV mortality and major bleeding (Catalano et al, 2007). A large randomised clinical trial, 'Aspirin for Asymptomatic Atherosclerosis', evaluated the use of aspirin 100mg daily versus placebo in individuals with asymptomatic PAD with an ABI ≤ 0.95. The study recruited almost 28,980 patients and results found no difference in CV

outcomes in patients on aspirin or those taking the placebo (Fowkes et al, 2010). Results from such studies challenge the efficacy of aspirin in PAD and what should be the optimal antithrombotic therapy in PAD (Feldman and Moussa, 2009).

A potential risk for platelet aggregation and thrombosis may be present when the patient is on antiplatelet treatment. Aspirin works by blocking cyclo-oxygenase and decreasing platelet activation. There are other important pathways for platelet activation that are not affected by aspirin (Robless et al, 2003). It is not clear if the role of antiplatelet medication affects the sequelae of PAD. Death rates in PAD patients remain quite high and use of antiplatelet therapy provides at best only modest effects with regards to limb salvage and long-term patency rates in patients who undergo endovascular and surgical procedures (Azarbal et al, 2015).

1.7.2 Current guidelines for antithrombotic therapy in peripheral artery disease

The American Heart Association/American College of Cardiology (AHA/ACC) Guidelines 2016 recommend the use of antiplatelet therapy alone in symptomatic PAD patients for the reduction of MI, stroke and vascular death. Aspirin at a dose of 75mg to 325mg per day or clopidogrel at a dose of 75mg is recommended. The effectiveness of using two anti-platelet agents to minimise the cardiovascular risk in patients with symptomatic PAD is not well established. In asymptomatic individuals with an ABI of ≤ 0.90, the use of antiplatelet therapy is reasonable to decrease the risk of MI, stroke or vascular death. For asymptomatic patients who have a borderline ABI of 0.91-0.99 the use of antiplatelet therapy is still uncertain (Gerhard-Herman et al, 2017).

The European Society of Cardiology (ESC) 2017 guidelines, suggest the use of single antiplatelet therapy in symptomatic patients with lower extremity arterial disease or in patients who undergone revascularisation. According to ESC guidelines, clopidogrel is the preferred drug in lower extremity arterial disease (Aboyans et al, 2017). Evidence from a study carried out by the Antithombotic Trialists' Collaboration (2002) supports the use of aspirin or any other antiplatelet agent to protect patients against MACE who are at an increased risk of occlusive vascular events such as in PAD (Antithrombotic Trialists' Collaboration, 2002).

Analysing and targeting other pathways by using new medication such as NOACs can further decrease the risk of CV events in patients with PAD (Tsipis et al, 2014). To date NOACs are not indicated for use in patients with PAD. Clinical trials on the use of NOACs for new indications such as PAD, are ongoing. Studies will help establish the role of NOACs in PAD and if the indications of NOACs can be further expanded.

1.8 Rational of the study

The rational of the study was to present a comparative approach between the conventional antithrombotic medication: aspirin, and the more recently approved antithrombotic medications: the NOACs, in terms of safety profiles.

Aspirin is the drug of choice for secondary prevention in patients with PAD. The efficacy of aspirin may vary between PAD patients. In view of varied efficacy of aspirin, other antithrombotic medications need to be identified as alternatives. NOACs may be potential substitutes for aspirin.

The study will help to identify health outcomes following intake of NOACs in patients with PAD and asses if NOACs have the potential to be used in this patient cohort.

1.9 Aims

To conduct a comparative analysis of ADRs reported for aspirin and ADRs reported for NOACs and to identify studies on the off-label use of NOACs in patients with PAD.

1.9.1 Objectives

- To identify and compare ADRs as documented in PV reports for aspirin, apixaban, dabigatran and rivaroxaban
- To observe ADRs following the use of aspirin and NOACs in the Maltese population and compare them to ADRs from PV reports
- To identify studies on the use of NOACs in PAD
- To analyse patient accessibility to NOACs

Chapter 2

Methodology

2.1 Study overview

The study was divided into five phases. Figure 2.1 shows a flow chart of the study.

1. Pharmacovigilance (PV) reports were used to analyse adverse drug reactions (ADRs) for aspirin and for the novel oral anticoagulants (NOACs) apixaban, dabigatran and rivaroxaban.
2. A questionnaire was developed and validated and used to collect information from the Maltese population on ADRs encountered by patients while taking aspirin or either apixaban, dabigatran and rivaroxaban.
3. Documented ADRs from PV reports were compared to reported ADRs from patients.
4. A literature search was carried out to identify studies on the use of NOACs in off-label use for peripheral artery disease (PAD).
5. Accessibility of NOACs was evaluated by using the local hospital formulary to identify which NOACs are procured through the national health services. The cost of the three NOACs available in Malta was compared.

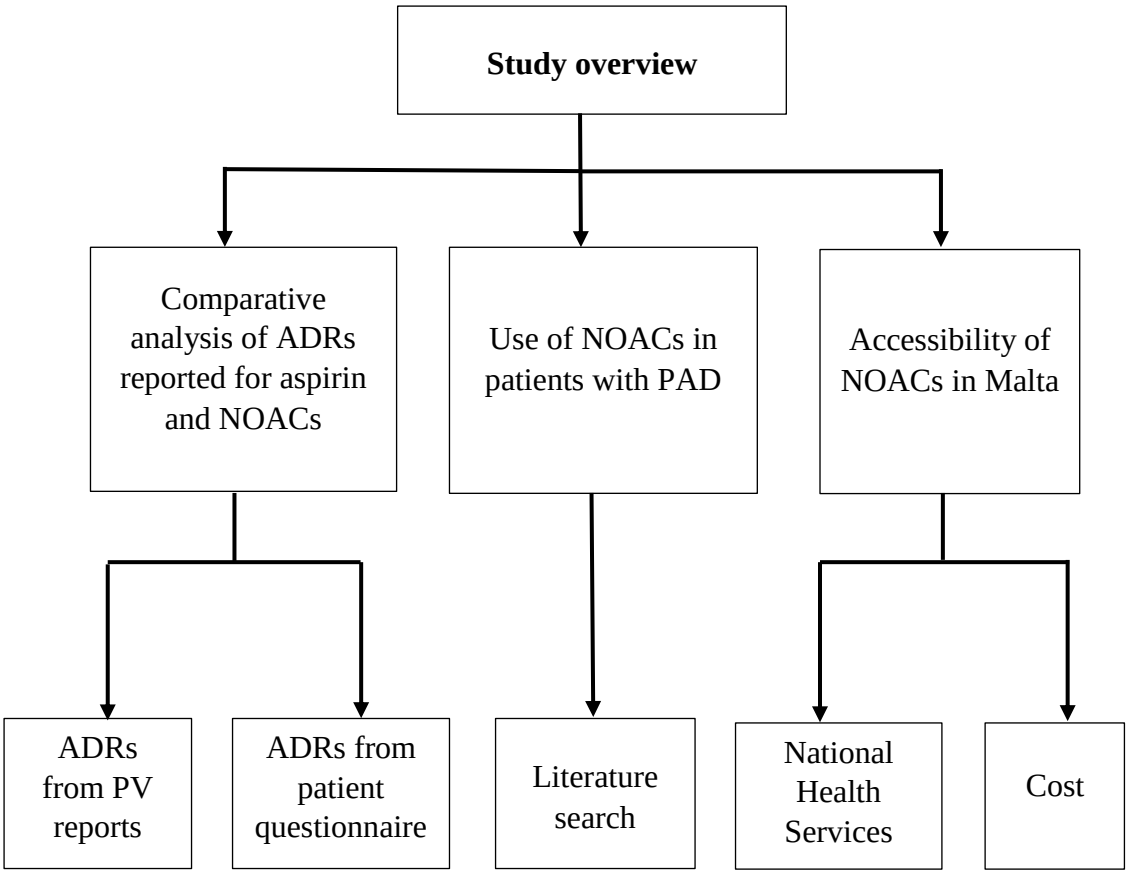

Figure 2.1: Study overview

2.2 Identification of ADRs

A total of fifteen ADRs were chosen to be analysed. The Summaries of Product Characteristics (SPC) of aspirin, apixaban, dabigatran and rivaroxaban were downloaded from the Electronic Medicines Compendum (eMC) website. Section 4.8 of each of the four SPCs was reviewed so as to identify which ADRs were listed as commonly occurring. Section 4.8 of each SPC is related to ADRs of the drugs. ADRs which were classified as being 'common' on the SPCs were compiled in a list. Some of the ADRs

were considered as 'common' in more than one of the four drugs under investigation. The compiled list was analysed and from it fifteen ADRs were chosen as the ADRs to be used for analysis in the study. The fifteen ADRs were chosen for analysis on the basis of which ADRs were common to more than one drug and ADRs which could be easily identified by the patient or documented on the patient's file, and did not involve laboratory values such as haemoglobin levels and liver function tests. ADRs were listed according to the Medical dictionary for Regulatory Activities (MedRA) preferred term so as to ensure that the same terminology was used throughout the study to avoid confusion. MedDRA is a standardised medical dictionary used to facilitate the sharing of regulatory information for medical products intended for human consumption (Merrill, 2008).

2.3 Pharmacovigilance reports – Phase 1

PV reports were used to identify and analyse spontaneously reported ADRs for aspirin, apixaban, dabigatran and rivaroxaban.

2.3.1 Identifying frequency of reported adverse drug reactions

The Eudravigilance Data Analysis System (EVDAS) was used to assess ADRs which were reported for aspirin and for the three NOACs; apixaban, dabigatran and rivaroxaban, which are marketed in Malta[6]. EVDAS is a component of eudravigilance which contains

[6] Muscat C. 2018, Personal communication, 6th February 2018.

data used for pharmacovigilance safety activitities. PV reports were used to analyse reported cases of the fifteen chosen ADRs for aspirin, apixaban, dabigatran and rivaroxaban. The ADRs of the NOACs were compared with the ADRs for aspirin.

The Eudravigilance website, www.eudra.org, was used to obtain the PV reports. EVDAS was used and a screening procedure was applied retrospectively to extract all the reports on rivaroxaban, dabigatran and apixaban for the fifteen ADRs. The time frame considered, was from when reports started being collected by Eudravigilance (1995) until the beginning of September 2017, the time when the reports were extracted. PV reports for rivaroxaban were obtained until 4th September 2017, while that for apixaban and for dabigatran until 11th September 2017. PV reports for aspirin were obtained until the 12th September 2017. For analysis, individual reported cases for the fifteen chosen ADRs for the four medications were obtained from EVDAS in the form of Individual Case Line Listing (ICLL). Each ICLL gave a summary about the reported ADR. ICLL included information such as the patient's medication history, age, gender, seriousness of the ADR and a brief summay of events following intake of medication. Cases of ADRs reported between the years 2013 to 2017 were used for the comparative analysis between the four medications. Reported cases between 2013 and 2017 were chosen for analysis so as to ensure a fair comparison between the four medications. From the three investigated NOACs, apixaban was the last approved NOACs in 2012.

The ICLLs were obtained by choosing Eudravigilance Query Libraries from EVDAS followed by Pharmacovigilance Query Library, Individual Case Listings and Enhanced Individual Case Line Listing (options which can be chosen from EVDAS database and

lead to the opening of ICLLs). The drug under investigation was chosen from a list of medications in the database together with one of the ADRs under investigation. The procedure was repeated fifteen times with the same medication, but choosing a different ADR each time. ADRs were coded according to MedDRA. The report to obtain the ICLLs was performed using all the EudraVigilance Post-authorisation Module Individual Case Safety Reports (EVPM ICSRs) which were spontaneously submitted to Eudravigilance. The procedure was repeated for all the four medications; aspirin, apixaban, dabigatran and rivaroxaban and was used to identify the reported cases on the fifteen ADRs studied. For aspirin, the term acetylsalicylic acid was used while for the other drugs, the terms apixaban, dabigatran and rivaroxaban were used. The EVPM ICSRs provide information on the ADRs encountered per individual patient. The report provide data on the patient characteristics, medication history, a brief summary of the occurrence of the ADR and the seriousness of the ADR. The number of reports of ADRs are continuously being updated according to the number of new cases being reported to the European Medicines Agency (EMA).

2.3.2 Analysis of Pharmacovigilance Reports

For analysis, data extracted from EVDAS was inputted in Microsoft® Excel. The reported cases were analysed and comparisons between ADRs following the use of aspirin and ADRs following the use of NOACs; apixaban, dabigatran and rivaroxaban were carried out. Reported cases were analysed in terms of seriousness of events, frequency of reported ADRs and patient characteristics including age and gender.

2.4 Development, Validation and Administration of Questionnaire – Phase 2

For the second phase of the study, a questionnaire was developed and validated and was used to collected information from patients who were either taking aspirin or NOACs.

2.4.1 Approvals

The second phase of the study was carried out at Mater Dei Hospital (MDH). Necessary approvals were obtained from the Data Protection Officer, the Chief Executive Officer and the Head of Surgery of MDH. Approval to carry out the study was granted from the University Research and Ethics Committee (UREC) (Protocol number: 35/2017) (Appendix 1).

2.4.2 Patient Information Sheet

A Patient Information Sheet (Appendix 2) was prepared to provide information on the research study for patients. The Patient Information Sheet described the aims of the research and contained a summary of the study. Two versions of the Patient Information Sheet were prepared, one in English and one in Maltese. Patients were informed that all data provided will be kept confidential. Patients recruited for the study were given a unique code to ensure anonymity.

2.4.3 Patient Consent Form

A Patient Consent Form was prepared and was available both in Maltese and English (Appendix 3). The consent form contained information on the research and showed that patients were giving consent to the investigator to use the provided information for the purpose of the study. Patients were informed that results from the study were to be used for medical and scientific purposes. Participation in the study was voluntary and participants could withdraw from the study at any time without providing any reason. The consent form was signed by the patient participating in the study.

A three digit code was assigned to the enrolled patients thereby ensuring anonymity. The code written on the Patient Consent Form was unique to every patient and served to identify patients.

2.4.4 Patient Questionnaire

A patient questionnaire was developed in English and Maltese to help collect information from patients admitted to hospital in surgical wards (Appendix 4). The semi-structured questionnaire consisted of fifteen questions divided into two sections.

The first section of the questionnaire consisted of seven questions related to demographic information, smoking habits, physical activity, medical history and drug history. The

second section of the questionnaire was composed of eight questions related to information about aspirin or NOACs and related ADRs. The second section contained questions about patient's perception and concerns related to intake of medication. Patients responded questions in the second section using a five point likert scale or by using 'Yes', 'No' or 'Do not know' options. For each patient, the questionnaire carried the same three digit code as the one used on the patient consent form.

The main focus of the questionnaire was to identify any ADRs encountered following administration of aspirin or NOACs. The fifteen ADRs which were chosen from PV reports to be investigated were included in the questionnaire. For the purpose of the questionnaire, gastrointestinal pain and abdominal pain were grouped as one term, to avoid confusion for the patient. If any of the fourteen ADRs was experienced by the patient following intake of aspirin or NOACs, the ADR had to be classified according to the severity; mild, moderate or severe. Table 2.1 shows the classification of ADRs according to severity. Patients were also asked about any other ADRs encountered while on aspirin or NOACs and these ADRs were listed as 'Others'.

Table 2.1: Classification for severity of adverse drug reactions. (adapted from Day RS, Hubal R. Understanding the Frequency and Severity of Side Effects: Linguistic, Numeri c, and Visual Representations. AAAI Spring Symposium - Technical Report. 2006;6(1): 69-75).

Severity of ADR	
Mild	Bothersome, requiring no change in therapy, no medical attention
Moderate	Needs change in therapy, additional treatment, dangerous, serious, worrisome, requires hospitalisation
Severe	Disabling, life-threatening

2.4.5 Validation of Questionnaire

A validation panel was appointed to analyse and provide feedback on the developed questions for the questionnaire. Healthcare professionals were contacted via electronic mail and asked if they would be interested in being part of the validation panel. The validation panel consisted of seven members; three doctors, three pharmacists and a lay person. The doctors who agreed to be part of the validation panel were a consultant and a higher specialist trainee working in vascular surgery and a basic specialist trainee working in medicine. The pharmacists who participated included a clinical pharmacist, a community pharmacist and a pharmacist working in the regulatory field. Feedback provided by members of the validation panel was analysed and modifications to the questionnaire were implemented based on suggestions made by the members of the validation panel.

2.4.6 Inclusion/Exclusion criteria

Patients enrolled in the study were men and women who were at least eighteen years of age and were surgical in-patients at MDH. Patients were to have a clear understanding of either Maltese or English. Patients had to be either taking aspirin or any one of the three NOACs under investigation. The patients had to be able to communicate with the investigator, hold an adequate verbal conversation and speak clearly. Patients who showed confusion, had hearing impairment or had dementia were excluded from the study.

2.4.7 Data Collection from wards

Patients for the study were chosen by convenience sampling. A total of nine surgical wards were identified as having the potential candidates for the study. These wards are Surgical Wards 1 to 5, Neuro-Surgical Ward, Cardiac Surgical Ward, Surgical Admission Unit and Orthopaedics Ward 2.

The study was carried out over a four month period. Data for the study was collected between September 2017 and January 2018. Patients' files were reviewed by the investigator to gather information and to assess if patients can be included in the study.

2.5 Analysis and comparison of data from Phase 1 and Phase 2

Data on reported ADRs obtained from PV reports for aspirin was compared to data obtained from PV reports for the three NOACS; rivaroxaban, dabigatran and apixaban. Differences in the number of cases of ADRs reported for the three NOACs were evaluated. Data from PV reports was compared to data collected from patient questionnaires. IBM SPSS version 24 was used to analyse the data. The Independent sample t-test, Chi-squared test, One-way analysis of variance (ANOVA), Two-way ANOVA and the tukey post hoc tests were used to analyse data, with p values <0.05 considered to show statistically significant differences. A logistic regression analysis was also used for data obtained from patient's questionnaires. The fifteen ADRs studied were divided into three categories for comparison. The categories were: bleeding-related ADRs

(contusion, epistaxis, eye haemorrhage, gastrointestinal haemorrhage and gingival bleeding), gastrointestinal ADRs (abdominal and gastrointestinal pain, constipation, diarrhoea, dyspepsia, nausea and vomiting) and central nervous system (CNS)-related events and hypotenion (dizziness, headache and hypotension).

2.6 Studies on the use of novel oral anticoagulants in peripheral artery disease

A literature search was conducted to identify any studies on the off-label use of NOACs in PAD. Search engines and websites were used for the search. The literature search was done to identify studies of patients with PAD, randomised to either one of the available NOACs and which reported efficacy and safety outcomes following use of NOACs.

Websites[7-9] were used to get access to a number of completed or ongoing clinical trials. Other resources used for the search, included PubMed and the Cochrane Library which provided access to databases such as Medline and the Cochrane Central Register of Controlled Trials (CENTRAL). ProQuest and HyDi system of the University of Malta website were used to retrieve other relevant research studies. HyDi provided access to various databases which lead to a number of scientific journals and articles. Some of the databases researched for potentially relevant studies included Academic Search Complete, CINAHL Plus, and ScienceDirect. The clinical trials and research studies

[7] ClinicalTrials.gov [Online]. U.S. National Library of Medicine. [cited 2018 April 27]. Available from: https://clinicaltrials.gov/.
[8] UK Clinical Trials Gateway [Online]. National Institute for Health Research. [cited 2018 April 27]. Available from: https://www.ukctg.nihr.ac.uk/.
[9] TrialResults-Center.org [online]. TrialResults Center. [cited 2018 April 27]. Available from: http://www.trialresultscenter.org/.

included were used to investigate the off-label use of any one of the NOACs in patients with PAD.

A variety of keywords and phrases related to the search topic were used to carry out the search. Examples of keywords used included 'apixaban', 'dabigatran', 'edoxaban', 'rivaroxaban' 'peripheral artery disease and rivaroxaban', 'novel oral anticoagulants in artery disease', 'NOACs in vascular disease', 'off-label use of novel oral anticoagulants' 'anticoagulants in peripheral artery disease', 'use of dibagatran in peripheral artery disease' and 'apixaban and arterial disease'. The search for relevant trials and research studies was conducted until April 2018.

2.7 Identification of available novel oral anticoagulants in Malta – national health services

The latest online version (28th December 2017) of the national health services formulary list was retrieved from the government website health.gov.mt. Two formularies were available; the hospital formulary and the out-patients formulary. The hospital formulary consisted of a list of medicinal products, vitamins, food supplements and borderline substances which can be prescribed for patients who are admitted in hospital as in-patients. The out-patients formulary contained pharmaceutical products which patients are entitled to through the national health services, and are dispensed to out-patients free of charge. The formularies consist of all the non-proprietary names, dosage forms and dosage strength of medicinal products which are available for patients through the national health services. For some medications, patients require a permit to be entitled

for the medication. Medications which require a permit are linked to a medicine protocol. A medicine protocol specifies the criteria when a particular medicinal product should be used. Both the hospital formulary and the out-patients formulary were used to identify if any of the NOACs, apixaban, dabigatran, rivaroxaban are available through the national health services and indications for use.

2.8 Identification of available novel oral anticoagulants in Malta – the private sector

The regulatory authority in Malta; the Malta Medicines Authority was contacted to identify which NOACs are licensed to be used in Malta and are available in the private sector.

The local medical representative agents of the NOACs apixaban, dabigatran and rivaroxaban were contacted by email to gain information on NOACs available on the Maltese market. Information on the dosage strengths, the pack size per box and the cost of the medication was attained.

2.9 Statistical Analysis

Data from PV reports and from questionnaires was inputted into IBM SPSS® Statistics Version 24 and Microsoft Excel® 2013. A number of statistical tests were used to assess

differences between reported ADRs occurring after intake of aspirin or NOACs, from PV reports and questionnaires.

2.9.1 Independent Sample T-Test

The Independent Sample T-Test was used to compare the means between two independent groups. The Independent Sample T-test was used to compare the mean patient age of patients on aspirin and patients on rivaroxaban. The Null hypothesis (H_0) specified that the mean ages of the two groups of patients was similar and was accepted if the p-value exceeded the 0.05 level of significance. The Alternative hypothesis (H_1) specified that ages differ significantly between the two groups and was accepted if the p-value was less than 0.05 criterion.

2.9.2 Chi-Square Test

The Chi-Square Test was used to analyse the association between two categorical variables. One of the variables described the medicine taken (aspirin/NOACs) and the other variable described gender, smoking habits, physical activity and the presence or absence of an ADR. The Null hypothesis (H_0) specified that there was no association between the two categorical variables and was accepted if the p-value exceeded the 0.05 level of significance. The Alternative hypothesis (H_1) specified that there was a significant association between the two categorical variables and was accepted if the p-value was less than 0.05 criterion.

2.9.3 Logistic Regression Analysis

Logistic regression analysis was used to analyse the association between one dependent binary variable and one or more independent variables. The logistic regression analysis was a predictive analysis.

The major limitation of the chi-square test was that it investigated solely the association between two categorical variables. The aim of many research studies is to analyse the association between several variables collectively. The use of a statistical model such as logistic regression analysis permited that several variables can be analysed.

A binary logistic regression model was fitted for the dependent variable (occurrence of ADRs following intake of aspirin or rivaroxaban). The variable is categorical and participants of the study had to select one of two options – Yes/No. The dependent variable was related for predictors which include age, gender, smoking status and the number of chronic medications.

2.9.4 One–way analysis of variance

The One-way analysis of variance (ANOVA) was used to assess the presence of statistically significant differences between the means of three or more groups. The one-way ANOVA analysed one independent categorical variable and one continuous

dependent variable. The Null hypothesis (H_0) determined that there was no association between the groups and was accepted if the p-value exceeded the 0.05 level of significance. The Alternative hypothesis (H_1) determined that there was a significant association between the groups and was accepted if the p-value was less than 0.05 criterion.

2.9.5 Two-way analysis of variance

The Two-way ANOVA is similar to the one-way ANOVA. The two-way ANOVA assessed the influence of two categorical independent variables on one continuous dependent variable. A p-value greater than 0.05, showed no statistical significance between the groups while a p-value less than 0.05, showed a statistically significant difference.

2.9.6 Tukey Post Hoc Test

The Tukey post hoc test was used together with the one-way ANOVA and two-way ANOVA to analyse if there was a significant difference between all possible pairs of means. The test was used for multiple comparisons. The Tukey post hoc test was used for the pairwise comparisons of aspirin, apixaban, dabigatran and rivaroxaban. The one-way and two-way ANOVA tests determined if an overall statistical significanct difference was present, while the Tukey post hoc test determined where the statistical difference, if any, between the medications pairwise. A p-value greater than 0.05, showed no statistical

significant difference between the groups while a p-value less than 0.05, showed a statistically significant difference.

2.10 Abstract Submissions

An abstract was submitted to the X Malta Medical School Conference 2018. Another abstract was submitted to the European Association of Hospital Pharmacists Congress 2018 (Appendix 7).

Chapter 3

Results

3.1 Identified Adverse Drug Reactions

A total of fifteen adverse drug reactions (ADRs) occurring following the administration of aspirin, apixaban, dabigatran or rivaroxaban were chosen for analyses from the Summary of Product Characteristics (SPCs) of the four medications investigated. Table 3.1 shows the list of the chosen ADRs.

Table 3.1: Analysed adverse drug reactions for aspirin, apixaban, dabigatran and rivaroxaban.

Adverse Drug Reaction
Abdominal pain
Constipation
Contusion
Diarrhoea
Dizziness
Dyspepsia
Epistaxis
Eye Haemorrhage
Gastrointestinal Haemorrhage
Gastrointestinal Pain
Gingival Bleeding
Headache
Hypotension
Nausea
Vomiting

3.2 Analysis of Pharmacovigilance Reports

All the reported cases received by Eudravigilance, for the fifteen ADRs, until early September 2017 when data extraction was carried out, were considered for analysis. Reported cases for aspirin dated back to 1995. For apixaban reports dated back to 2010, for dabigatran reports dated back to 2005 and for rivaroxaban reports dated back to 2003. Cases consisted of reported ADRs following approval of medication for human consumption and ADRs occurring when medication was still under investigation. Up to early September 2017, a total number of 78,161 pharmacovigilance (PV) reports referring to the fifteen ADRs in Table 3.1 for the four medications under investigation were identified. ADRs were most commonly reported for rivaroxaban (n=34%). Apixaban had the least reported cases (n=6%) of ADRs. Table 3.2 shows the number of PV reports for the fifteen ADRs for the four medications.

Table 3.2: Total number of pharmacovigilance reports for the fifteen chosen adverse drug reactions (N= 78161)

Medication	Time frame (years) when ADRs were reported	Total reported ADRs	Percentage of total ADRs
Rivaroxaban	2003-2017	26768	34%
Dabigatran	2005-2017	24362	31%
Aspirin	1995-2017	22406	29%
Apixaban	2010-2017	4625	6%

PV reports showed that gastrointestinal bleeding was the most commonly reported ADR for aspirin (n=9,898) and for all the three NOACs; rivaroxaban (n=13,689), dabigatran (n=8,715) and apixaban (n=1,742). For rivaroxaban the total number of reported cases of gastrointestinal haemorrhage accounted for more than half (51.14%) of the PV reports

for rivaroxaban. Table 3.3 shows the number of PV reports identified for each one of the fifteen ADRs for the four medications analysed.

Table 3.3: Total reported adverse drug reactions from pharmacovigilance reports. (N= 78161)

	Number of Adverse Drug Reaction Reports			
Adverse Drug Reaction	**Aspirin (n=22406)**	**Apixaban (n=4625)**	**Dabigatran (n=24362)**	**Rivaroxaban (n=26768)**
Abdominal pain	854	90	742	458
Constipation	248	85	312	232
Contusion	568	341	1288	1252
Diarrhoea	707	211	1854	571
Dizziness	1118	357	1366	1236
Dyspepsia	340	41	3428	153
Epistaxis	3743	754	1913	4676
Eye haemorrhage	215	167	228	499
Gastrointestinal haemorrhage	9898	1742	8715	13689
Gastrointestinal pain	46	11	47	18
Gingival bleeding	352	113	446	900
Headache	795	257	1094	1121
Hypotension	879	107	558	470
Nausea	1279	233	1678	888
Vomiting	1364	116	693	605

Epistaxsis was the second most commonly reported ADR for rivaroxaban (n=4676), aspirin (n=3743) and apixaban (n=754). For dabigatran the second most commonly reported ADR was dyspepsia with a total of 3428 PV reports. Gastrointestinal pain was the least commonly reported ADR for dabigatran (n=47), aspirin (n=46), rivaroxaban (n=18) and apixaban (n=11).

3.2.1 Patient characteristics of pharmacovigilance reports

Each PV report provided information about the patient who encountered one of the fifteen studied ADR following administration of either aspirin, apixaban, dabigatran or rivaroxaban. The 78,161 PV reports for aspirin, apixaban, dabigatran and rivaroxaban were analysed with regards to patient characteristics including age and gender and the seriousness of the ADR. PV reports provided data on whether the ADR was considered serious or not serious. Seriousness of an ADR was classified as either related to death, life-threatening, hospitalisation, disabling, congenital or other.

3.2.1.1 Age

Following analysis of the PV reports the mean age of patients for each of the fifteen ADRs were identified for the four medications. Some of the reports (n=14825) did not contain information regarding the patient's age. Table 3.4 shows the mean ages of patients in PV reports.

Table 3.4: Mean age of patients in pharmacovigilance reports for the fifteen adverse drug reactions (N =63336)

	Aspirin		Apixaban		Dabigatran		Rivaroxaban	
ADR	**Mean Age**	**NA**	**Mean Age**	**NA**	**Mean Age**	**NA**	**Mean Age**	**NA**
Abdominal pain	62.91	55	73.84	4	73.73	109	67.48	59
Constipation	70.09	21	76.22	16	75.21	35	70.49	29
Contusion	71.35	54	74.89	49	77.57	243	72.5	278
Diarrhoea	65.69	49	74.93	30	74.59	362	70.79	74
Dizziness	64.33	83	73.39	41	74.95	246	69.64	172
Dyspepsia	65.35	38	69.88	7	74.04	844	68	28
Epistaxis	72.52	174	76.53	103	76.64	429	72.12	892
Eye haemorrhage	69.52	45	76.64	52	76.14	57	74.09	170
GI haemorrhage	71.57	1569	77.85	553	77.83	2843	72.02	3181
GI pain	62.18	18	65.36	0	74.03	11	62.21	4
Gingival bleeding	67.92	41	74.08	18	74.69	83	69.49	193
Headache	60.33	74	70.8	39	72.03	215	66.46	145
Hypotension	64.43	40	73.32	13	75.85	40	70.48	40
Nausea	61.3	102	71.4	27	74.2	336	67.46	108
Vomiting	58.21	88	76.31	7	74.8	132	70.27	57

Mean age – shows the mean age of patients in years; NA – Not available - shows the number of reports which did not contain information about the patient's age; GI - Gastrointestinal

The mean age of patients who experienced an ADR was highest for patients on dabigatran (75 years), while the lowest mean age was for patients taking aspirin (66 years). The one-way analysis of variance (ANOVA) showed a statistically significant difference (p-value = 0.000) between the mean age of patients having an ADR following intake of one of the four medications under investigation.

3.2.1.2 Gender

PV reports were used to assess gender distribution. Table 3.5 shows the number of reports which stated the patients' gender. Table 3.5 shows the number of males and females who had one of the fifteen ADRs following the intake of aspirin or one of the NOACs. Some of the reports (n=5787) did not include the patients' gender and are not included in Table 3.5.

Table 3.5: Gender distribution in pharmacovigilance reports. (N=72374)

	Aspirin		**Apixaban**		**Dabigatran**		**Rivaroxaban**	
ADR	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**
Abdominal pain	449	386	57	33	391	315	257	195
Constipation	130	116	50	34	164	141	136	94
Contusion	312	240	198	138	735	511	641	532
Diarrhoea	375	318	124	82	923	826	332	229
Dizziness	563	546	170	179	692	627	679	544
Dyspepsia	178	144	22	19	1678	1458	79	72
Epistaxis	1406	2268	354	373	844	934	2123	2316
Eye haemorrhage	89	111	82	78	106	102	245	232
GI haemorrhage	3598	5263	775	768	3652	3652	6084	6181
GI pain	33	11	6	5	22	21	12	6
Gingival bleeding	135	201	69	40	236	178	430	431
Headache	430	348	168	85	579	461	654	454
Hypotension	388	466	57	49	299	253	234	229
Nausea	714	546	154	76	984	599	576	295
Vomiting	760	581	68	46	409	242	352	232
Total	**9560**	**11545**	**2354**	**2005**	**11714**	**10320**	**12834**	**12042**

ADR, Adverse Drug Reaction; F, Female; M, Male; GI, Gastrointestinal

For aspirin, there was a higher number of ADRs reported for males (11545), while for apixaban, dabigatran and rivaroxaban a higher number of ADRs was reported for the female gender. The one-way ANOVA test showed that no statistically significant difference was present between the number of ADRs reported for males ($p = 0.343$) and the number of ADRs reported for females ($p = 0.229$) between the four medications.

3.2.2 Seriousness of adverse drug reactions

Apart from patients' information and data on the ADR, PV reports provided information on whether the occurrence of the ADR was considered as being serious or not (Yes/No options). Table 3.6 shows the number of reports where the ADR was considered as being serious or not serious. For aspirin there were 137 reports where the seriousness of the ADR was not stated.

Table 3.6: Seriousness of adverse drug reactions. (N=78024)

	Seriousness of ADRs							
	Aspirin		Apixaban		Dabigatran		Rivaroxaban	
ADR	**S**	**NS**	**S**	**NS**	**S**	**NS**	**S**	**NS**
Abdominal pain	796	49	82	8	343	399	430	28
Constipation	231	16	81	4	118	194	222	10
Contusion	523	43	331	10	530	758	1233	19
Diarrhoea	668	34	186	25	491	1363	505	66
Dizziness	1061	44	316	41	417	949	1137	99
Dyspepsia	273	62	29	12	397	3031	129	24
Epistaxis	2252	1483	668	86	873	1040	4434	242
Eye haemorrhage	201	10	165	2	89	139	12	487
GI haemorrhage	9835	25	1740	2	7568	1147	13679	10
GI pain	45	1	8	3	15	32	16	2
Gingival bleeding	287	65	100	13	155	291	837	63
Headache	728	59	213	44	325	769	1013	108
Hypotension	869	6	106	1	491	67	462	8
Nausea	1157	97	190	43	460	1218	791	97
Vomiting	1298	51	110	6	349	344	579	26

S, Serious; NS, Not Serious; GI, Gastrointestinal

Gastrointestinal haemorrhage was the most commonly reported ADR with the greatest number of PV reports which were considered as having serious consequences to the patient for all the four medications. Following gastrointestinal haemorrhage, epistaxis was the ADR with the second highest number of PV reports which were considered as being serious for all the four medications evaluated. The one-way ANOVA test showed a statistically significant difference between the four medications for the number of ADR reports considered as not serious (p-value = 0.000). No statistically significant difference was observed between ADR reports considered as being serious (p-value = 0.379) for the four medications.

3.2.3 Evaluation of pharmacovigilane reports received between 2013 and 2017

The one-way ANOVA and two-way ANOVA tests were used to assess if there was any statistical significant difference between the fifteen chosen ADRs for aspirin, apixaban, dabigatran and rivaroxaban. To ensure a fair comparison between the four medications, PV reports between 2013 and the beginning of September 2017 were used. From the three NOACs investigated, apixaban was the last NOACs which has been approved for use in 2012 (Rose and Bar, 2018). Very few PV reports for apixaban (n=23) were older than 2013 and were not used for comparison. Table 3.7 shows the total number of PV reports for the fifteen ADRs between 2013 and beginning of September 2017.

Table 3.7: Pharmacovigilance reports per year for the fifteen analysed adverse drug reactions (N = 51391)

	2013	**2014**	**2015**	**2016**	**Until September 2017**	**Total**
Aspirin	2445	2090	2942	3526	1655	12658
Apixaban	175	567	1161	1541	1158	4602
Dabigatran	2801	2520	1017	1517	1444	9299
Rivaroxaban	3191	3702	6230	8233	3476	24832

For the fifteen studied ADRs, rivaroxaban (N=24,832) was the medication with the highest number of reported ADRs between the years 2013 and September 2017. Apixaban (N=4,602) was the medication which had the least number of reported cases for the fifteen studied ADRs. Averaged across five years, the mean number of reported ADRs was

highest for rivaroxaban (4966.40) as shown in Table 3.8. The second highest mean is for aspirin (2531.60) followed by dabigatran (1859.80) and apixaban (920.40).

Table 3.8: Mean number of pharmacovigilance reports between 2013-2017

Medication	Mean number of PV reports per year	Standard deviation
Aspirin	2531.60	729.417
Apixaban	920.40	543.139
Dabigatran	1859.80	761.977
Rivaroxaban	4966.40	2193.137
$F(3,16) = 9.618$, $p = 0.001$		

The one-way ANOVA test showed that there was a significant difference in the mean number of reported ADRs between the four medications, the highest reported ADRs were for rivaroxaban (N=24832). The difference between the means was significant since the p-value (0.001) was less than the 0.05 level of significance.

The tukey post hoc test was used to further analyse the results obtained in the one-way ANOVA test. The tukey post hoc test was used to compare the total number of ADRs reported yearly between the medications pairwise. Results from the tukey post hoc test show which two medications caused the statistically significant difference in the one-way ANOVA test. Table 3.9 shows results from the tukey post hoc test.

Table 3.9: Tukey post hoc test comparing medication pairwise

	Medication	Mean difference	Standard Error	P-value
Aspirin	Apixaban	1611.2	788.512	0.214
	Dabigatran	671.8	788.512	0.829
	Rivaroxaban	-2434.8	788.512	0.032
Apixaban	Aspirin	-1611.2	788.512	0.214
	Dabigatran	-939.4	788.512	0.641
	Rivaroxaban	-4046.0	788.512	0.001
Dabigatran	Aspirin	-671.8	788.512	0.829
	Apixaban	939.4	788.512	0.641
	Rivaroxaban	-3106.6	788.512	0.006
Rivaroxaban	Aspirin	2434.8	788.512	0.032
	Apixaban	4046.0	788.512	0.001
	Dabigatran	3106.6	788.512	0.006

The mean reported ADRs for rivaroxaban was significantly higher than the mean reported ADRs for the other medications. When comparing the p-values for rivaroxaban to any one of the other three medications, the p-values are less the 0.05 level of significance. When comparing rivaroxaban to aspirin the p-value is 0.032, for rivaroxaban and apixaban the p-value is 0.001 and for rivaroxaban and dabigatran the p-value is 0.006. For the other combinations with aspirin, apixaban and dabigatran, the mean reported ADRs do not differ significantly because the p-value is greater than the 0.05 level of significance.

The two-way ANOVA was used to assess if there was any association between the mean reported ADRs, the medication and the type of ADR. The two independent variables were the fifteen ADRs and the four medications. The amount of cases reported for the fifteen ADRs during the five years, were used as the dependent variable. Tables 3.10, 3.11 and 3.12 show the results of the two-way ANOVA test.

Table 3.10: Analysis of reported adverse drug reactions using the two-way analysis of variance test for bleeding-related adverse drug reactions

ADR	Medication	Mean	Standard Deviation	P-value
Contusion	Aspirin	73.40	15.805	0.000
	Apixaban	67.60	37.786	
	Dabigatran	74.00	44.497	
	Rivaroxaban	221.80	68.722	
Epistaxis	Aspirin	565.00	123.707	0.000
	Apixaban	150.40	101.125	
	Dabigatran	133.40	66.639	
	Rivaroxaban	875.20	292.591	
Eye haemorrhage	Aspirin	25.40	7.092	0.000
	Apixaban	33.40	22.131	
	Dabigatran	13.60	4.219	
	Rivaroxaban	94.80	18.593	
Gastrointestinal bleeding	Aspirin	1171.00	558.501	0.014
	Apixaban	348.40	198.793	
	Dabigatran	1064.20	474.794	
	Rivaroxaban	2594.80	1746.242	
Gingival bleeding	Aspirin	50.00	18.014	0.000
	Apixaban	22.60	13.539	
	Dabigatran	25.00	6.856	
	Rivaroxaban	161.20	54.380	

Table 3.11: Analysis of reported adverse drug reactions using the two-way analysis of variance test for gastrointestinal adverse drug reactions

ADR	Medication	Mean	Standard Deviation	P-value
Abdominal pain	Aspirin	70.00	7.517	0.000
	Apixaban	17.80	10.159	
	Dabigatran	56.60	19.781	
	Rivaroxaban	82.60	16.876	
Constipation	Aspirin	26.20	7.050	0.002
	Apixaban	17.00	11.726	
	Dabigatran	17.00	9.772	
	Rivaroxaban	43.20	11.256	
Diarrhoea	Aspirin	66.80	13.989	0.006
	Apixaban	41.80	26.687	
	Dabigatran	80.80	22.410	
	Rivaroxaban	101.60	26.207	
Dyspepsia	Aspirin	31.00	5.958	0.000
	Apixaban	8.20	5.119	
	Dabigatran	101.40	29.871	
	Rivaroxaban	26.00	11.769	
Gastrointestinal pain	Aspirin	6.40	2.408	0.017
	Apixaban	2.20	2.280	
	Dabigatran	2.60	1.517	
	Rivaroxaban	3.00	1.732	
Nausea	Aspirin	99.20	18.171	0.000
	Apixaban	46.20	22.819	
	Dabigatran	66.40	26.726	
	Rivaroxaban	147.60	36.644	
Vomiting	Aspirin	105.60	21.431	0.000
	Apixaban	23.00	14.799	
	Dabigatran	48.00	13.874	
	Rivaroxaban	102.60	31.174	

Table 3.12: Analysis of reported adverse drug reactions using the two-way analysis of variance test for central nervous system-related events and hypotension adverse drug reactions

ADR	Medication	Mean	Standard Deviation	P-value
Dizziness	Aspirin	95.40	6.348	0.000
	Apixaban	70.40	47.679	
	Dabigatran	54.40	24.224	
	Rivaroxaban	225.80	66.391	
Headache	Aspirin	85.00	9.874	0.002
	Apixaban	51.20	30.302	
	Dabigatran	50.00	15.620	
	Rivaroxaban	201.80	53.082	
Hypotension	Aspirin	61.20	9.418	0.056
	Apixaban	20.20	11.628	
	Dabigatran	72.40	64.500	
	Rivaroxaban	84.40	24.886	

A statistically significant difference between the mean reported ADRs and the medication used was seen for all the fifteen ADRs apart from hypotension. No statistically significant difference (0.056) was seen between hypotension and the four medications. The p-value was slightly greater than the 0.05 level of significance. The two-way ANOVA was followed by the tukey post hoc test to analyse if there was any statistically difference between each ADR and two medication pairs. Sections 3.2.3.1 to 3.2.3.15 show a comparative analysis between medications for the number of reported cases for each ADR between the years 2013 to 2017. Results from the tukey post hoc tests which show

statistically significant differences between pairwise comparisons are shown. Tables showing full results from the Tukey post hoc test are found in Appendix 5.

3.2.3.1 Abdominal pain

The amount of PV reports reported for abdominal pain for the medications investigated are shown in Table 3.13. Apixaban had the lowest number of reported cases of abdominal pain per year.

Table 3.13: Reported cases of abdominal pain. (N=1135)

Abdominal pain					
Number of PV reports according to year					
	2013	**2014**	**2015**	**2016**	**2017**
Aspirin	65	74	79	72	60
Apixaban	4	10	26	26	23
Dabigatran	73	82	47	45	36
Rivaroxaban	88	92	102	71	60

The tukey post hoc test showed that when comparing all possible pairs of mediations, the mean reported number of patients with abdominal pain was statistically significantly different for apixaban compared to either aspirin, dabigatran or rivaroxaban. The mean number of PV reports for abdominal pain was significantly higher for apixaban than for all the other medications as the p-values for apixaban-medication pairs are less than the 0.05 level of significance as shown in Table 3.14.

Table 3.14: Significant differences in reported cases for abdominal pain.

ADR-Abdominal pain			
Medication pairs	**Mean difference**	**Std .Error**	**P-value**
Apixaban - Aspirin	52.200	9.142	0.000
Apixaban - Dabigatran	-38.800	9.142	0.003
Apixaban - Rivaroxaban	-64.800	9.142	0.000

3.2.3.2 Constipation

The amount of reported cases for constipation are shown in Table 3.15.

Table 3.15: Reported cases of constipation. (N=517)

Constipation					
Number of PV reports according to year					
	2013	**2014**	**2015**	**2016**	**2017**
Aspirin	25	34	33	20	19
Apixaban	3	10	14	31	27
Dabigatran	27	28	8	13	9
Rivaroxaban	44	45	56	46	25

The tukey post hoc test demonstrated that a statistically significant difference was present between the mean reported cases for constipation following intake of rivaroxaban compared to patients taking either apixaban (p-value=0.004) or dabigatran (p-value=0.04). Table 3.16 shows medication pairs with statistically significant differences for constipation.

Table 3.16: Significant differences in reported cases for constipation.

ADR-Constipation			
Medication pairs	**Mean difference**	**Std .Error**	**P-value**
Rivaroxaban-Apixaban	26.200	6.398	0.004
Rivaroxaban-Dabigatran	26.200	6.398	0.004

3.2.3.3 Contusion

The amount of cases reported for contusion are shown in Table 3.17. Rivaroxaban had the largest number of reported cases for contusion.

Table 3.17: Reported cases for contusion. (N=2184)

Contusion					
Number of PV reports according to year					
	2013	**2014**	**2015**	**2016**	**2017**
Aspirin	67	78	80	92	50
Apixaban	6	63	73	101	95
Dabigatran	131	113	44	35	47
Rivaroxaban	175	236	281	288	129

A statistically significant difference was observed between the mean reported cases of contusion following intake of rivaroxaban compared to the mean reported cases for aspirin, apixaban and dabigatran. The tukey post hoc test gave p-values smaller than the 0.05 level of significance for pairwise combinations of rivaroxaban as shown in Table 3.18.

Table 3.18: Significant differences in reported cases for contusion.

ADR-Contusion			
Medication pairs	**Mean difference**	**Std .Error**	**P-value**
Rivaroxaban-Aspirin	148.400	28.949	0.001
Rivaroxaban-Apixaban	154.200	28.949	0.000
Rivaroxaban-Dabigatran	147.800	28.949	0.001

3.2.3.4 Diarrhoea

Table 3.19 shows the number of reported cases for diarrhoea, with rivaroxaban having the largest number of reported cases.

Table 3.19: Reported cases for diarrhoea. (N=1455)

Diarrhoea					
Number of PV reports according to year					
	2013	**2014**	**2015**	**2016**	**2017**
Aspirin	73	75	74	70	42
Apixaban	9	30	58	78	34
Dabigatran	97	109	68	77	53
Rivaroxaban	96	130	112	110	60

For diarrhoea, the only statistical significant difference was observed between the medication pair apixaban and rivaroxaban (Table 3.20). The tukey post hoc test gave a p-value of 0.004, which is smaller than the 0.05 criterion.

Table 3.20: Significant differences in reported cases for diarrhoea.

ADR-Diarrhoea			
Medication pairs	**Mean difference**	**Std .Error**	**P-value**
Apixaban-Rivaroxaban	-59.800	14.481	0.004

3.2.3.5 Dizziness

The number of reported cases of patients having dizziness after intake of either aspirin, apixaban, dabigatran or rivaroxaban are shown in Table 3.21.

Table 3.21: Reported cases for dizziness. (N=2230).

Dizziness					
Number of PV reports according to year					
	2013	**2014**	**2015**	**2016**	**2017**
Aspirin	105	98	91	89	94
Apixaban	13	30	86	128	95
Dabigatran	94	57	51	37	33
Rivaroxaban	208	261	299	238	123

The tukey post hoc test showed that a statistically significant difference was present between the mean reported cases for dizziness when comparing rivaroxaban to the other three medications investigated as shown in Table 3.22.

Table 3.22: Significant differences in reported cases for dizziness.

ADR-Dizziness			
Medication pairs	**Mean difference**	**Std .Error**	**P-value**
Rivaroxaban-Aspirin	130.400	27.033	0.001
Rivaroxaban-Apixaban	155.400	27.033	0.000
Rivaroxaban-Dabigatran	171.400	27.033	0.000

3.2.3.6 Dyspepsia

The numbers of reported cases for dyspepsia are shown in Table 3.23. Dabigatran had the greatest number of reported cases for dyspepsia.

Table 3.23: Reported cases of dyspepsia. (N=833)

Dyspepsia					
Number of PV reports according to year					
	2013	**2014**	**2015**	**2016**	**2017**
Aspirin	36	35	35	25	24
Apixaban	2	4	9	12	14
Dabigatran	121	128	99	107	52
Rivaroxaban	26	18	38	37	11

The difference in mean reported cases for dyspepsia was statistically significantly different between pairwise combination of dabigatran and each of the other three medications; aspirin (p-value = 0.000), apixaban (p-value=0.000) and rivaroxaban (p-value=0.000). Table 3.24 shows results from the tukey post hoc test for medication pairs with statistical significance for dyspepsia.

Table 3.24: Significant differences in reported cases for dyspepsia.

ADR-Dyspepsia			
Medication pairs	**Mean difference**	**Std .Error**	**P-value**
Dabigatran-Aspirin	70.400	10.452	0.000
Dabigatran-Apixaban	93.200	10.452	0.000
Dabigatran-Rivaroxaban	75.400	10.452	0.000

3.2.3.7 Epistaxis

Table 3.25 shows the number of reported cases for epistaxis following intake of aspirin and the three NOACs. Rivaroxaban had the largest number of reported cases for epistaxis.

Table 3.25: Reported cases of epistaxis. (N=8620)

Epistaxis					
Number of PV reports according to year					
	2013	**2014**	**2015**	**2016**	**2017**
Aspirin	529	538	673	695	390
Apixaban	21	68	198	261	204
Dabigatran	229	178	84	94	82
Rivaroxaban	702	808	1075	1261	530

Epistaxis was the ADR which showed the most statistically significant differences between medication pairs. Following the tukey post hoc test, p-values showed statistical significant differences between the mean reported cases of epistaxis when comparing aspirin to either apixaban or dabigatran or rivaroxaban. Statistical significance was observed between all rivaroxaban medication pairs and shown in Table 3.26.

Table 3.26: Significant differences in reported cases for epistaxis.

ADR-Epistaxis			
Medication pairs	**Mean difference**	**Std .Error**	**P-value**
Aspirin-Apixaban	414.600	107.508	0.007
Aspirin-Dabigatran	431.600	107.508	0.005
Aspirin-Rivaroxaban	-310.200	107.508	0.048
Rivaroxaban-Apixaban	724.800	107.508	0.000
Rivaroxaban-Dabigatran	741.800	107.508	0.000

3.2.3.8 Eye Haemorrhage

The numbers of reported cases for eye haemorrhage are shown in Table 3.27.

Table 3.27: Reported cases for eye haemorrhage. (N=836)

Eye haemorrhage					
Number of PV reports according to year					
	2013	**2014**	**2015**	**2016**	**2017**
Aspirin	25	33	32	20	17
Apixaban	4	23	36	64	40
Dabigatran	19	17	11	12	9
Rivaroxaban	82	98	111	113	70

The p-values smaller than the 0.05 level of significance (Table 3.28) showed a statistically significant differences between mean reported cases for eye haemorrhage for rivaroxaban when compared to reported cases for aspirin, apixaban and dabigatran.

Table 3.28: Significant differences in reported cases for eye haemorrhage.

ADR-Eye Haemorrhage			
Medication pairs	**Mean difference**	**Std .Error**	**P-value**
Rivaroxaban-Aspirin	69.400	9.506	0.000
Rivaroxaban-Apixaban	61.400	9.506	0.000
Rivaroxaban-Dabigatran	81.200	9.506	0.000

3.2.3.9 Gastrointestinal Haemorrhage

The numbers of PV reports for gastrointestinal haemorrhage are shown in Table 3.29 with rivaroxaban having the largest number of reported cases.

Table 3.29: Reported cases for gastrointestinal haemorrhage. (N=25892)

Gastrointestinal haemorrhage					
Number of PV reports according to year					
	2013	**2014**	**2015**	**2016**	**2017**
Aspirin	1097	674	1409	2002	673
Apixaban	76	227	447	585	407
Dabigatran	1670	1379	438	908	926
Rivaroxaban	1079	1222	3294	5291	2088

The tukey post hoc test showed a statistically significant difference in the mean number of reported cases for gastrointestinal bleeding between rivaroxaban and apixaban. A p-value of 0.009 (Table 3.30) was obtained, hence the difference in means was significant.

Table 3.30: Significant differences in reported cases for gastrointestinal haemorrhage.

ADR-Gastrointestinal Haemorrhage			
Medication pairs	**Mean difference**	**Std .Error**	**P-value**
Rivaroxaban-Apixaban	2246.400	602.182	0.009

3.2.3.10 Gingival Bleeding

The amount of reported cases of ginigival bleeding are shown in Table 3.31.

Table 3.31: Reported cases for gingival bleeding. (N=1294)

Gingival bleeding					
Number of PV reports according to year					
	2013	**2014**	**2015**	**2016**	**2017**
Aspirin	47	62	57	64	20
Apixaban	4	17	26	41	25
Dabigatran	33	32	20	20	20
Rivaroxaban	193	183	192	173	65

The mean reported cases of gingival bleeding was significantly different when comparing the means of reported cases for rivaroxaban to any one of the other three medications. The tukey post hoc test showed p-values of 0.000 for the three medication pairs as shown in Table 3.32.

Table 3.32: Significant differences in reported cases for gingival bleeding.

ADR-Gingival Bleeding			
Medication pairs	**Mean difference**	**Std .Error**	**P-value**
Rivaroxaban-Aspirin	111.200	18.740	0.000
Rivaroxaban-Apixaban	138.600	18.740	0.000
Rivaroxaban-Dabigatran	136.200	18.740	0.000

3.2.3.11 Gastrointestinal Pain

The amount of PV reports for gastrointestinal pain are shown in Table 3.33. Gastrointestinal pain was the ADR with the lowest number of reports between the years 2013 and 2017.

Table 3.33: Reported cases for gastrointestinal pain. (N=71)

Gastrointestinal pain					
Number of PV reports according to year					
	2013	**2014**	**2015**	**2016**	**2017**
Aspirin	9	5	5	4	9
Apixaban	0	2	2	6	1
Dabigatran	2	3	5	1	2
Rivaroxaban	3	4	4	4	0

For gastrointestinal pain, the tukey post hoc test showed a statistically significant difference in the mean reported cases for aspirin, compared to apixaban (p-value= 0.022) and dabigatran (p-value=0.040). Table 3.34 shows medication pairs with statistical significance for gastrointestinal pain.

Table 3.34: Significant differences in reported cases for gastrointestinal pain.

ADR-Gastrointestinal Pain			
Medication pairs	**Mean difference**	**Std .Error**	**P-value**
Aspirin-Apixaban	4.200	1.277	0.022
Aspirin-Dabigatran	3.800	1.277	0.040

3.2.3.12 Headache

The numbers of reported PV reports for headache are shown in Table 3.35.

Table 3.35: Reported cases for headache. (N=1940)

Headache					
Number of PV reports according to year					
	2013	**2014**	**2015**	**2016**	**2017**
Aspirin	80	88	97	89	71
Apixaban	9	29	71	71	76
Dabigatran	69	59	28	51	43
Rivaroxaban	179	222	265	219	124

The tukey post hoc test showed a statistically significant difference between the mean reported cases for patients suffering from headache following intake of rivaroxaban, compared to patients on either aspirin, apixaban or dabigatran. Rivaroxaban medication pairs showing statistically significant differences are found in Table 3.36.

Table 3.36: Significant differences in reported cases for headache.

ADR-Headache			
Medication pairs	**Mean difference**	**Std .Error**	**P-value**
Rivaroxaban-Aspirin	116.800	20.193	0.000
Rivaroxaban-Apixaban	150.600	20.193	0.000
Rivaroxaban-Dabigatran	151.800	20.193	0.000

3.2.3.13 Hypotension

The numbers of reported cases for hypotension are shown in Table 3.37.

Table 3.37: Reported cases for hypotension. (N=1191)

Hypotension					
Number of PV reports according to year					
	2013	**2014**	**2015**	**2016**	**2017**
Aspirin	60	67	72	60	47
Apixaban	6	12	23	36	24
Dabigatran	76	183	40	32	31
Rivaroxaban	69	98	103	104	48

A statistically significant difference was observed following the pairwise comparison of mean reported cases for hypotension following intake of apixaban and the mean reported cases for hypotension following intake of rivaroxaban. A p-value (0.049) slightly smaller than the 0.05 level of significance was observed as shown in Table 3.38.

Table 3.38: Significant differences in reported cases for hypotension.

ADR-Hypotension			
Medication pairs	**Mean difference**	**Std .Error**	**P-value**
Apixaban-Rivaroxaban	-64.200	22.369	0.049

3.2.3.14 Nausea

The amount of reported cases for nausea are shown in Table 3.39.

Table 3.39: Reported cases for nausea. (N=1797)

Nausea					
Number of PV reports according to year					
	2013	**2014**	**2015**	**2016**	**2017**
Aspirin	113	101	103	111	68
Apixaban	15	30	62	69	55
Dabigatran	102	88	43	48	51
Rivaroxaban	165	173	161	156	83

Pairwise comparison showed a statistically significant difference in the mean reported cases of nausea in patients taking apixaban compared to patients taking aspirin or rivaroxaban. A difference in means was observed between pairwise comparison of dabigatran and rivaroxaban as shown in Table 3.40.

Table 3.40: Significant differences in reported cases for nausea.

ADR-Nausea			
Medication pairs	**Mean difference**	**Std .Error**	**P-value**
Apixaban-Aspirin	-53.000	17.053	0.031
Apixaban-Rivaroxaban	-101.400	17.053	0.000
Dabigatran-Rivaroxaban	-81.200	17.053	0.001

3.2.3.15 Vomiting

Table 3.41 shows the number of reported cases for vomiting, with aspirin having the largest number of reported cases over the five years.

Table 3.41: Reported cases for vomiting. (N=1396)

Vomiting					
Number of PV reports according to year					
	2013	**2014**	**2015**	**2016**	**2017**
Aspirin	114	128	102	113	71
Apixaban	3	12	30	32	38
Dabigatran	58	64	31	37	50
Rivaroxaban	82	112	137	122	60

The tukey post hoc test showed a significant difference between the mean reported cases for vomiting in patients taking aspirin compared to patients taking either apixaban (p-value=0.000) or dabigatran (p-value=0.003). A difference in means was observed between pairwise comparisons of rivaroxaban to either apixaban or dabigatran. Table 3.42 shows medication pairs with statistical significance for vomiting.

Table 3.42: Significant differences in reported cases for vomiting.

ADR-Vomiting			
Medication pairs	**Mean difference**	**Std .Error**	**P-value**
Aspirin-Apixaban	82.600	13.574	0.000
Aspirin-Dabigatran	57.600	13.574	0.003
Rivaroxaban-Apixaban	79.600	13.574	0.000
Rivaroxaban-Dabigatran	54.600	13.574	0.005

3.3 Analysis of patient questionnaire

A total of fifty patients who met the inclusion criteria and accepted to participate in the questionnaire were recruited for the study. Twenty-five patients were taking aspirin and twenty-five were on rivaroxaban. During the study period no patients on apixaban or dabigatran were identified. For the patient's questionnaire comparisons were done for aspirin and rivaroxaban. Statistical tests were used to carry out comparisons between patients on aspirin and patients on rivaroxaban

3.3.1 Demographic Data

The first section of questionnaire collected demographic information on the patients participating in the study.

3.3.1.1 Gender

From a total of fifty patients enrolled for the study, twenty-two patients were female and twenty-eight patients were male. Table 3.43 shows the distribution of patients taking aspirin and rivaroxaban.

Table 3.43: Gender distribution between aspirin and rivaroxaban (N=50)

		Gender	
		Male	**Female**
Medication (N=50)	**Aspirin** (n=25)	15	10
	Rivaroxaban (n=25)	7	18
$X^2(1) = 5.195$, $p = 0.023$			

There was a statistically significant difference between patient gender and patients on aspirin or rivaroxaban ($p = 0.023$).

3.3.1.2 Age

The mean age for the total population enrolled in the study was 70.1 years Patients who were in the aspirin group had a mean age of 69.92 years (range 47-91) and those in the rivaroxaban group had a mean age of 70.28 years (range 52-87).

The independent group t-test showed no significant difference ($p = 0.902$) between the mean age group of patients on aspirin and patients on rivaroxaban. The mean age of patients on aspirin was similar to the mean age of patients on rivaroxaban. There was no evidence that the type of medication taken depends on the age of the patient. The greatest

number of patients who participated in the study were aged between seventy one and eighty (20 patients).

3.3.2 Smoking status and physical activity

Data about smoking status and physical activity for patients enrolled for the questionnaire were comparable for patients taking aspirin and patients taking rivaroxaban. The chi-squared test showed no statistical significance difference for smoking status (p value = 0.062) and for physical activity (p value = 0.274).

3.3.3 Chronic Medications

The number of chronic medication (including aspirin and rivaroxaban) per patient ranged from one to fifteen different types of medication. Table 3.44 shows the number of chronic medications administered to patients.

Table 3.44: Patient medication intake (N=50)

Number of medication (including aspirin and rivaroxaban)	Number of patients
1 – 4	8
5 – 8	29
More than 8	13

The most frequently prescribed chronic medications were diuretics (n=34), followed by statins (n=32) and oral hypoglycaemic agents (n=27). Figure 3.1 shows chronic medications taken by patients who participated in the questionnaire. 'Other' chronic

medications not included in the figure include medications such as antiepileptics, digoxin, and vitamin/mineral supplements

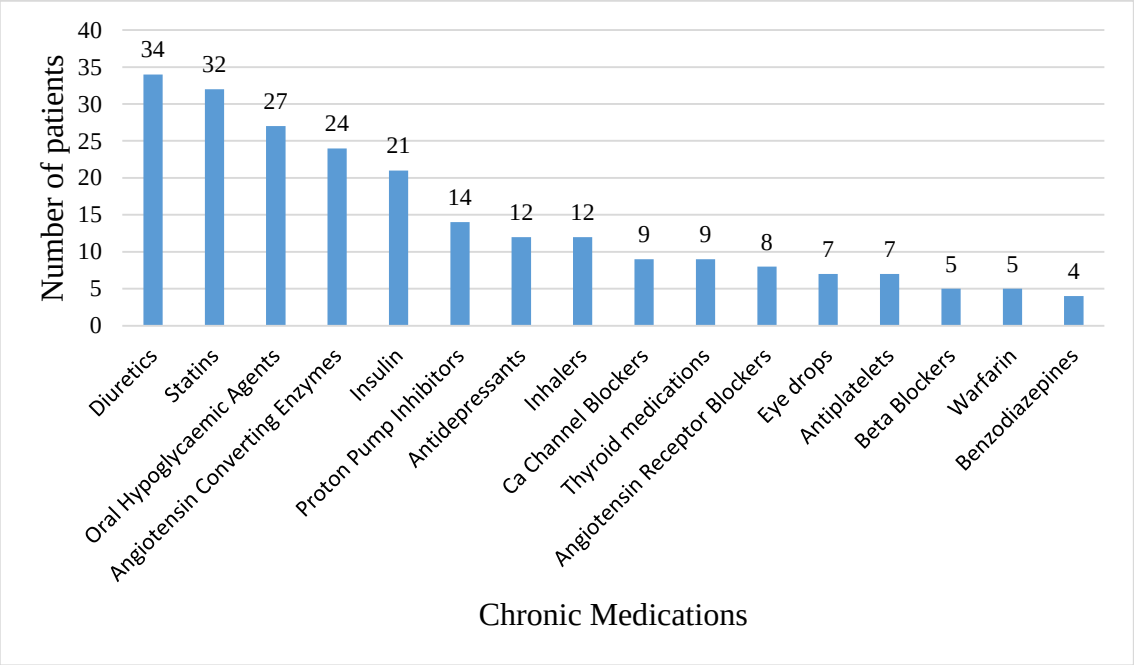

Figure 3.1: Chronic medications excluding aspirin, rivaroxaban and 'other' medications.

3.3.4 Indications for aspirin and rivaroxaban

Patients in the aspirin cohort were given aspirin for secondary prevention of cardiac events. Patients were given aspirin at a dose of 75mg daily. Aspirin was indicated for secondary prevention in patients with diabetes, peripheral artery disease (PAD) and cardiac disease such as coronary artery disease (CAD) and ischaemic heart disease (IHD).

The majority of patients on rivaroxaban (n=49) were given the medication as thomboprophylaxis for the prevention of venous thromboembolism following total knee replacement (TKR) or total hip replacement (THR). The dose of rivaroxaban was 10mg

once daily. One of the patients was started on a dose of 10mg daily, but the dose was increased to 20mg daily for one month due to some complications encountered during the stay in hospital.

One of the patients on rivaroxaban was given the medication for treatment of bilateral pulmonary embolism (PE). The treatment dose was of 15mg twice a day for three weeks for acute management of PE. After three weeks, the dose was changed to 20mg daily. The 20mg dose was used to treat PE and for the prevention of recurrent PE.

3.3.5 Reported adverse drug reactions from patients

From the fifty patients recruited for the study, thirty-six patients (72%) stated that they had at least one ADR following the administration of aspirin (18 patients) or rivaroxaban (18 patients). Fourteen patients (28%) reported no ADR following the administration of aspirin or rivaroxaban. During data collection from questionnaires, patients reported ADRs following intake of either aspirin or rivaroxaban which were not included in the fifteen ADRs investigated. Table 3.45 shows the number of patients who reported the occurrence of an ADR.

Table 3.45: Number of patients reporting ADRs with aspirin or rivaroxaban

		Medication	
		Aspirin	**Rivaroxaban**
Any ADRs following the start of aspirin/rivaroxaban	**Yes**	18	18
	No	7	7
$X^2(1) = 0.000$, $p = 1.000$			

The chi-squared test showed no statistically significant difference (p = 1.000) between reported ADRs for aspirin and reported ADRs for rivaroxaban. The occurrence of ADRs was comparable for aspirin and rivaroxaban as the p-value (1.000) exceeded the 0.05 level of significance. There was no evidence that the occurrence of ADRs after starting aspirin or rivaroxaban varies between the two groups.

The percentage of males having an ADR after starting medication (72.7%) was comparable to the percentage of females (71.4%). The chi-square test showed no statistical significant difference (p value = 0.919). There was no evidence that the occurrence of ADRs after starting aspirin or rivaroxaban varies between genders. In the age range between seventy one and eighteen years (14 patients) there was the highest number of patients who reported at least one ADR following the administration of aspirin or rivaroxaban. This was followed by patients in the age range between sixty-one and seventy years (11 patients). The chi-square test showed no statistically significant difference between age groups and the occurrence of ADR.

Patients taking between five to eight chronic medications (n=23) were the most patients who reported the occurrence of an ADR following intake of either aspirin or rivaroxaban. The chi-square test showed no statistically significant difference between the number of chronic medication intake and ADRs occuring following intake of aspirin or rivaroxaban.

3.3.5.1 Logistic regression analysis for the occurrence of adverse drug reactions and several variables

The pseudo R-square value (0.342) showed that the four predictor model explains 34.2% of the total variation of responses obtained when patients were asked about the occurrence of ADRs following intake of aspirin and rivaroxaban (Question 10a of the questionnaire). The remaining 65.8% of the total variation is explained by other predictors which were not included in the study. Examples of predictors which could affect the occurrence of an ADR include the dose of the antithrombotic medication, dosage regimen, food intake and hepatic and renal impairment.

The logistics regression model identifies smoking status as the best predictor of the responses of Question 10a (Did the patient encounter any ADR after starting aspirin or NOACs?) as the lowest p-value (0.014) was obtained. Smoking status was followed by age (p-value = 0.138), gender (p-value = 0.331) and number of chronic medications (p-value = 0.670). Smoking status was the only significant variable since the p-value is less than the 0.05 level of significance (Table 3.46).

Table 3.46: Data from logistic regression model

Variable	Model Fitting Criteria -2 Log Likelihood	Chi-square value	Degress of freedom	p-value
Age	37.515	5.510	3	0.138
Gender	32.951	0.947	1	0.331
Smoking status	40.589	8.584	2	0.014
Number of chronic medication	32.806	0.801	2	0.670

The parameter estimate B (Table 3.47) for patients aged sixty years or less (3.066) is larger than the parameter estimate B of other age categories indicating that patients aged sixty years or less have more ADRs than other patients in older age groups. The difference is significant as the p-value (0.037) is smaller than the 0.05 level of significance.

The parameter estimate B for males (-0.913) is smaller than the parameter estimate B of females indicating that the occurrence of ADRs for male patients is less than the occurrence of ADRs for female patients. The difference was not statistically significant.

The parameter estimate B for smokers (-4.076) is smaller than the parameter estimate B of the other smoking status categories indicating that the occurrence of ADRs in smokers is less than the occurrence of ADRs than non-smokers or previous smokers. The difference is significant and not attributed to chance as the p-value (0.015) is smaller than the 0.05 criterion.

The parameter estimate B for patients taking between 1-4 medications (-0.819) is smaller than the parameter estimates of other chronic medications categories indicating that patients taking less medications have less ADRs than patients taking more medication (Table 3.47). The difference is not significant. The odds ratios show the association between the occurrence of an ADR and a variable.

Table 3.47: Parameter estimates for variables used in logistic regression analysis.

	Parameter estimates			
Variable	**B (co-efficient)**	**Std. Error**	**P-value**	**Odds Ratio**
Age = ≤60 years	3.066	1.471	0.037	21.456
Age = 61-70 years	2.201	1.302	0.091	9.030
Age = 71-80 years	1.400	1.095	0.201	4.053
Age = More than 80 years	0	.	.	.
Gender = Male	-0.913	0.952	0.338	0.401
Gender = Female	0	.	.	.
Smoking status = Non-smoker	-2.079	1.424	0.144	0.125
Smoking status = Smoker	-4.076	1.675	0.015	0.017
Smoking status = Previous smoker	0	.	.	.
Number of chronic medication = 1-4	-0.819	1.093	0.454	0.441
Number of chronic medication = 5-8	0.069	0.858	0.936	1.071
Number of chronic medication = More than 8	0	.	.	.

3.3.6 Adverse drug reactions and severity

For the chosen ADRs analysed in the patient questionnaire, patients reported forty-seven ADRs for aspirin (62.6%) and twenty eight ADRs for rivaroxaban (37.3%). Patients reported ADRs as being either mild or moderate. None of the patients reported having a severe ADR following intake of aspirin or rivaroxaban. There was fifty-nine instances where the ADR was reported as mild and sixteen instances where the ADR was reported as being moderate in severity. Table 3.48 shows the severity of reported ADRs.

Table 3.48: Severity of reported adverse drug reactions (N=75)

		Medication	
		Aspirin (%)	**Rivaroxaban (%)**
Severity of reported ADRs	**Mild**	35 (74.5%)	24 (85.7%)
	Moderate	12 (25.5%)	4 (14.3%)
	Severe	0 (0.0%)	0 (0.0%)
$X^2(1) = 1.322$, p = 0.250			

There was a larger number of patients on rivaroxaban (85.7%) who reported the occurrence of an ADR with mild severity compared to the percentage of patients on aspirin (74.5%) who reported an ADR with mild severity. A larger percentage of patients on aspirin (25.5%) reported an ADR with moderate severity compared to patients on rivaroxaban (14.3%). The percentage difference (11.2%) between ADRs reported as being mild and ADRs reported as being moderate was not significant, since the p-value (0.250) exceeded the 0.05 level of significance. Figure 3.2 shows the percentage of ADRs which were reported as either mild or moderate. There were more ADRs which were reported as mild for both aspirin and rivaroxaban than ADRs which were considered as moderate in severity.

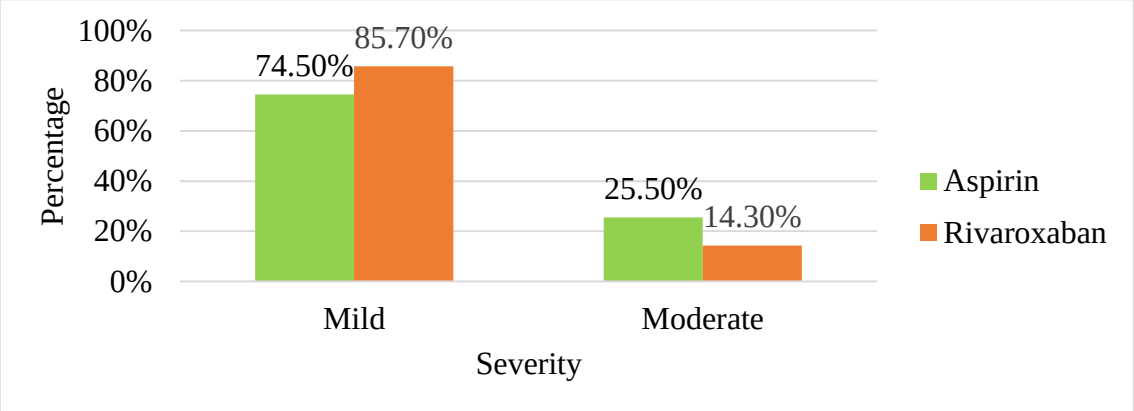

Figure 3.2: Reported adverse drug reactions according to severity

Table 3.49 shows the severity of each reported ADR for aspirin and rivaroxaban. Severity of ADR was reported according to table 2.1. For aspirin, constipation (n=7), dizziness (n=7) and headache (n=7) were the most commonly reported ADRs. For rivaroxaban, hypotension (n=6), constipation (n=5) and dizziness (n=4) were the most commonly reported ADRs.

Table 3.49: Reported adverse drug reactions from patients

	Medication					
	Aspirin			**Rivaroxaban**		
ADR	**N**	**Mild**	**Moderate**	**N**	**Mild**	**Moderate**
Abdominal and GI pain	1	1	0	0	0	0
Constipation	7	2	5	5	3	2
Contusion	4	3	1	2	2	0
Diarrhoea	2	2	0	0	0	0
Dizziness	7	7	0	4	4	0
Dyspepsia	3	2	1	2	1	1
Epistaxis	3	2	1	1	1	0
Eye haemorrhage	2	1	1	0	0	0
GI haemorrhage	2	2	0	0	0	0
Gingival bleeding	0	0	0	1	1	0
Headache	7	4	3	3	3	0
Hypotension	3	3	0	6	5	1
Nausea	5	5	0	3	3	0
Vomiting	1	1	0	1	1	0
Total	47	35	12	28	24	4

ADR, Adverse Drug Reaction; GI, Gastrointestinal; N, total number of reported ADRs,

The chi-squared test was used to analyse if there was an association between each one of the studied ADR and the intake of aspirin and rivaroxaban. For each individual ADR, no statistical significant difference was observed as the p-values all exceeded the 0.05 level

of significance. Results showed that for the study population the reported ADRs for aspirin are comparable to the reported ADRs for rivaroxaban.

3.3.7 Patient's perception and attitude on intake of aspirin or rivaroxaban

Two thirds of patients (n=33 patients) participating in the study knew why the medication was prescribed and understood the importance of taking aspirin or rivaroxaban. The majority of the patients (84%) enrolled in the study were not aware of the implications and risks associated with the concomitant use of anti-inflammatory medication and aspirin/rivaroxaban. There was 82% of patients who claimed that they rarely or never felt worried about experiencing ADRs related to the intake of aspirin or rivaroxaban. Approximately half of the participants (n=27 patients), said that they never or rarely felt worried about developing complications as a result of not taking aspirin or rivaroxaban prescribed for secondary prevention. The majority of patients (n=39 patients) understood the importance of informing healthcare professionals about the intake of aspirin or rivaroxaban prior to undergoing surgery or a procedure.

3.4 Comparison of adverse drug reactions from pharmacovigilance reports and questionnaire

Considering the number of reported cases for the fifteen ADRs investigated between the years 2013 and September 2017 (Table 3.8), the one-way ANOVA test showed a

statistically significant difference (p-value = 0.001) between the mean number of ADRs reported yearly for the four medications: aspirin, apixaban, dabigatran and rivaroxaban. The result from the one-way ANOVA test was used to identify which pairwise combinations of medication was causing a statistically significant difference. Results from the tukey post hoc test showed a statistically significant difference between the mean reported ADRs yearly for rivaroxaban versus aspirin (p-value = 0.032), rivaroxaban versus apixaban (p-value = 0.001) and rivaroxaban versus dabigatran (p-value = 0.006) (Table 3.9). From the four medications under investigation, rivaroxaban had the largest number of PV reports (n=24,832) for the fifteen analysed ADRs.

The fifteen ADRs studied were divided into three categories for comparison: bleeding-related ADRs (contusion, epistaxis, eye haemorrhage, gastrointestinal haemorrhage and gingival bleeding), gastrointestinal ADRs (abdominal and gastrointestinal pain, constipation, diarrhoea, dyspepsia, nausea and vomiting) and central nervous system (CNS) related events and hypotenion (dizziness, headache and hypotension).

Analyses of PV reports between 2013 and 2017, for aspirin and the three NOACs, showed that bleeding-related ADRs (N=38,826 or 75.6%) were the most frequently reported ADRs for all the four medications. Comparing the three NOACs, results showed that the largest number of ADRs reported cases were associated to bleeding-related ADRs (n=29,402) for all the three NOACs, rivaroxaban (n=19,739), dabigatran (n=6,551) and apixaban (n=3,112). Table 3.50 shows the percentages and number of reported cases for the bleeding-related ADRs, gastrointestinal ADRs and CNS-related and hypotension ADRs for aspirin, apixaban, dabigatran and rivaroxaban.

Table 3.50: Reported adverse drug reactions for bleeding-related, gastrointestinal and central nervous system related and hypotension adverse drug reactions

		Aspirin	**Apixaban**	**Dabigatran**	**Rivaroxaban**
		% (no. of PV reports)	% (no. of PV reports)	% (no. of PV reports)	% (no. of PV reports)
ADRs	Bleeding-related	74.5 (9424)	67.6 (3112)	70.4 (6551)	79.5 (19739)
	Gastrointestinal	16.0 (2026)	17.0 (781)	20.0 (1864)	10.2 (2533)
	CNS-related and hypotension	9.5 (1208)	15.4 (709)	9.6 (884)	10.3 (2560)

Gastointestinal bleeding was the most frequently reported ADR (N=25,892) for aspirin (n=5,855) and the three NOACs investigated, rivaroxaban (n=12,974), dabigatran (n=5,321) and apixaban (n=1,742). Epistaxis was the second most frequently reported ADR for aspirin (n=2,825) and for three NOACs. For rivaroxaban (n=4,376), apixaban (n=752) and dabigatran (n= 667). For rivaroxaban (n=1,129) and apixaban (n=352) the third most reported ADR was dizziness, while for dabigatran, dyspepsia (n=507) was the third most reported ADR. For aspirin, vomiting (n=528) was the three most frequently reported ADR. Gastrointestinal pain was the least reported ADR for all the four medications investigated, aspirin (n=32), apixaban (n=11), dabigatran (n=13) and rivaroxaban (n=15).

Statistical analysis of data obtained from PV reports for the years 2013 to 2017 was carried out to identify differences between each reported ADR and pairwise medication. The tukey post hoc test was used for pairwise analysis of medications. The test helped identify any statistically significant differences between the four medications and each one of the investigated ADRs. Results from the Tukey post hoc tests showed that aspirin

and the three NOACs, differ significantly in terms of reported ADRs. Table 3.51 shows the ADRs which showed statistically significant differences between medication pairs. Statistically significant difference between at least one medications pair was observed for each ADR studied.

Table 3.51: Adverse drug reactions with statistically significant differences between medication pairs

Medication Pair	ADRs with statistically significant differences between medication pairs (number of ADRs)
Aspirin versus Apixaban	abdominal pain, epistaxis, gastrointestinal pain, nausea, vomiting (n=5)
Aspirin versus Dabigatran	abdominal pain, dyspepsia, epistaxis, gastrointestinal pain, vomiting (n=5)
Aspirin versus Rivaroxaban	contusion, dizziness, epistaxis, eye haemorrhage, gingival bleeding, headache (n=6)
Apixaban versus Rivaroxaban	abdominal pain, constipation, contusion, diarrhoea, dizziness, epistaxis, eye haemorrhage, gastrointestinal bleeding, gingival bleeding, headache, hypotension, nausea, vomiting (n=13)
Apixaban versus Dabigatran	dyspepsia (n=1)
Dabigatran versus Rivaroxaban	constipation, contusion, dizziness, dyspepsia, epistaxis, eye haemorrhage, gingival bleeding, headache, nausea, vomiting (n=10)

Epistaxis was the ADR which had the largest number of pairwise medications (N=5) showing statistically significant differences (Table 3.26). Gastrointestinal haemorrhage was the most frequently reported ADR for all the four mediccations investigated but a statistical significant difference in the mean number of reported cases, was observed only between rivaroxaban and apixaban (Table 3.30). The medication pair apixaban and rivaroxaban had the largest number of ADRs (n=13) which showed a statistically significant difference between the number of reported PV cases. For the medication pair

apixaban and dabigatran a statistically significant difference (p-valaue = 0.000) between the mean number of reported ADRs, was only observed for dyspepsia.

Analysing the fifteen ADRs and comparing aspirin and rivaroxaban as documented in PV reports between 2013 and 2017, results showed that 33.8% (12,658 ADRs) of the reported cases of ADRs were following aspirin intake, while 66.2% (24,832 ADRs) of ADRs resulted following intake of rivaroxaban. When comparing reported ADRs for aspirin and rivaroxaban as reported in the patient questionnaire, 62.6% (47 ADRs) of reported ADRs resulted following intake of aspirin, while 37.3% (28 ADRs) of ADRs occurred following intake of rivaroxaban (Table 3.52).

Table 3.52: Reported adverse drug reactions for aspirin and rivaroxaban from pharmacovigilance reports and patient questionnaire.

	PV reports % (number of reports)	**Patient Questionnaire % (number of reported ADRs)**
Aspirin	33.8 (12,658)	62.6 (47)
Rivaroxaban	66.2 (24,832)	37.3 (28)

Analysing the results obtained from the questionnaire, thirty-six patients from the fifty enrolled in the study, encountered at least one ADR following intake of either rivaroxaban (n=18 patients) or aspirin (n = 18 patients). The number of patients on aspirin who had an ADR following intake of the medication was equal to the number of patients who had an ADR while taking rivaroxaban. The chi-squared test showed no statistically significant difference (p-value = 1.000) between reported ADRs for aspirin and reported ADRs for rivaroxaban (Table 3.45).

Analyses of PV reports between 2013 and 2017, for aspirin and rivaroxaban, showed that bleeding-related ADRs were the most frequently reported cases for aspirin and rivaroxaban. For aspirin, bleeding-related ADRs accounted for 74.5% (n=9,424 reported cases), gastrointestinal ADRs accounted for 16% (n=2,026 reported cases) and CNS-related events and hypotension accounted for 9.5% (n=1,208 reported cases) of the analysed ADRs. For rivaroxaban, bleeding-related ADRs accounted for 79.5% (n=19,739 reported cases), gastrointestinal ADRs accounted for 10.2% (n=2,533 reported cases) and CNS related events and hypotension accounted to 10.3% (n=2560 reported cases) of the analysed ADRs (Table 3.53).

Table 3.53: Comparison between aspirin and rivaroxaban.

		PV reports		**Patient Questionnaire**	
		Aspirin	**Rivaroxaban**	**Aspirin**	**Rivaroxaban**
		% (no. of PV reports)	% (no. of PV reports)	% (no. of reported cases)	% (no. reported cases)
ADRs	Bleeding-related	74.5 (9424)	79.5 (19739)	23.4 (11)	14.3 (4)
	Gastrointestinal	16.0 (2026)	10.2 (2533)	40.4 (19)	39.3 (11)
	CNS-related and hypotension	9.5 (1208)	10.3 (2560)	36.2 (17)	46.4 (13)

Analysis of reported ADRs from patient questionnaire showed that bleeding-related events were the least frequently reported ADRs for patients on aspirin and patients on rivaroxaban. For aspirin, bleeding-related ADRs accounted for 23.4% (n=11 reported cases), CNS-related ADRs and hypotension accounted for 36.2% (n=17 reported cases) and gastrointestinal ADRs accounted for 40.4% (n=19 reported cases) of the reported ADRs. For rivaroxaban, bleeding-related ADRs accounted to 14.3% (n=4 reported

cases), gastrointestinal ADRs accounted for 39.3% (n=11 reported cases) and CNS-related ADRs and hypotensios accounted for 46.4% (n=13 reported cases) of the reported ADRs.

PV reports showed that gastrointestinal haemorrhage was the most frequently reported ADR from the fifteen analysed ADRs for both aspirin (n=5,855 reported cases) and rivaroxaban (n=12,974 reported cases). No statistically significant difference between reported cases of gastrointestinal haemorrhage for aspirin and rivaroxaban was observed. Data gathered from the patient's questionnaire showed that there were two reported cases of gastrointestinal haemorrhage for patients taking aspirin. None of the patients who were on rivaroxaban reported gastrointestinal haemorrhage following intake of the medication. The chi-squared test showed no statistically significant difference between the reported cases of gastrointestinal haemorrhage for aspirin compared to patients on rivaroxaban.

Epistaxis was the second most frequently reported ADR in PV reports for both aspirin (n=2,825) and rivaroxaban (n=4,376). The tukey post hoc test showed a statistically significant difference (p-value =0.048) between the mean number of cases of epistaxis reported yearly for aspirin and rivaroxaban (Table 3.26). From the questionnaires, data showed that there were three patients who reported having epistaxis following intake of aspirin and one patient who reported epistaxis following intake of rivaroxaban. No statistical difference was observed.

When comparing aspirin and rivaroxaban from PV reports, the tukey post hoc test showed statistically significant differences in the number of reported ADRs for contusion,

dizziness, epistaxis, eye haemorrhage, gingival bleeding and headache. Identifed statistical significant differences between the reported cases of ADRs for contusion (p-value = 0.001) (Table 3.18), dizziness (p-value = 0.001) (Table 3.22), epistaxsis (p-value = 0.048) (Table 3.26), eye haemorrhage (p-value =0.000) (Table 3.28), gingival bleeding (p-value = 0.000) (Table 3.32) and headache (p-value = 0.000) (Table 3.36). Comparing data from the questionnaire for aspirin and rivaroxaban, the chi-square test showed no statistically significant differences between each ADR reported for aspirin compared to rivaroxaban. For the study population the reported ADRs for aspirin were comparable to the reported ADRs for rivaroxaban.

ADRs identified from patients' questionnaires, were classified as being mild, moderate or severe. Patients reported ADRs as being either mild or moderate in severity. None of the patients reported having a severe ADR following administration of either aspirin or rivaroxaban. A larger percentage of patients on rivaroxaban (85.7%) reported the occurrence of an ADR with mild severity compared to the percentage (74.5%) of patients on aspirin who reported an ADR with mild severity. A larger percentage of patients on aspirin (25.5%) reported an ADR with moderate severity when compared to individuals on rivaroxaban (14.3%) (Figure 3.2).

3.5 Studies on the use of novel oral anticoagulants in peripheral artery disease

Following a literature search a total of eight studies analysing the use of NOACs in patients with PAD were identified. The meta-analysis identified patients with PAD, treated with a NOAC compared to either aspirin, warfarin, clopidogrel or placebo. Five of the studies were on rivaroxaban, two on edoxoban and one on apixaban. No studies

on the use of dabigatran in patients with PAD were identified in literature. Further information on the identified studies is found in Appendix 6. Table 3.54 gives a summary of the efficacy and safety outcomes identified in the eight studies.

3.5.1 Studies on the use of apixaban in peripheral artery disease

Hu et al, 2017 – Apixaban versus warfarin

The risk of stroke or systemic embolism was comparable for patients given either apixaban or warfarin and who had PAD (hazard ratio: 0.63, 95% confidence interval: 0.32-1.25) and in patients without PAD (hazard ratio: 0.80, 95% confidence interval: 0.66-0.96, interaction p = 0.52). The effect of apixaban versus warfarin on all-cause death was comparable in PAD patients (HR 1.03, 95% CI 0.71–1.51) and in patinets without PAD (HR 0.88, 95% CI 0.78–0.99; interaction p=0.42). A statistical significant reduction in major or clinically relevant non-major bleeding in PAD patients was not observed when comparing apixaban to warfarin (hazard ratio: 1.05, 95% confidence interval: 0.69-1.58).

Conclusion: Comparable efficacy and safety.

3.5.2 Studies on the use of edoxaban in peripheral artery disease

Cunningham et al, 2016 - Edoxaban versus warfarin

In patients with PAD, the rates of stroke, systemic embolism and major bleeding were similar when patients were treated with either warfarin or high dose edoxaban. No significant differences were observed between treatment across a number of endpoints including stroke/systemic embolism (interaction p-value = 0.57), cardiovascular (CV) death (interaction p-value = 0.14), minor bleeding (interaction p-value = 0.54) and intracerebral haemorrhage (interaction p-value = 0.77). Patients on low dose edoxoban showed higher rates of stroke or systemic embolism compared to warfarin (p-interaction = 0.04).

Conclusion: High dose edoxaban has similar efficacy and safety to warfarin. Reductions in cardiovascular (CV) death and intracranial haemorrhage were observed with high dose edoxaban.

ePAD - Moll et al, 2018 – Edoxaban + aspirin versus clopidogrel + aspirin

In PAD patients underging revascularisation procedures the risk of major or life threatening bleeding was similar in patients taking edoxaban and aspirin compared to patients on clopidogrel and aspirin. The risk of restenosis or reocclusion was lower for patients with edoxaban and aspirin. A lower incidence of restenosis/reocclusion was observed with edoxaban compared to clopidogrel (95% CI 0.59 to 1.34, p-value = 0.643).

Conclusion: Similar risks for major and life-threatening bleeding events with edoxaban and aspirin compared to patients on clopidogrel and aspirin.

3.5.3 Studies on the use of rivaroxaban in peripheral artery disease

Jones et al, 2014 - Rivaroxaban versus warfarin

In terms of efficacy, rivaroxaban and warfarin were similar for the prevention of stroke or systemic embolism in PAD patients (hazard ratio: 1.19, 95% confidence interval: 0.63-2.22) and in patients without PAD (hazard ratio: 0.86, 95% confidence interval: 0.73-1.02). The p-value was 0.34. No other statistically significant difference were observed for rivaroraxban and warfarin for patients with or without PAD in any of the secondary efficacy endpoints such as myocardial infarction (MI) (p-value=0.49), vascular death (p-value= 0.26) and all-cause death (p-value=0.50). A statistically significant (p-value = 0.037) higher risk of major and non-major clinically relevant bleeding in individuals with PAD taking rivaroxaban compared to patients on warfarin (hazard ration: 1.40, 95% confidence: 1.06-1.86) and patients without PAD (hazard ratio: 1.03, 95% confidence interval: 0.95-1.11) was observed.

Conclusion: Similar efficacy, higher risk of bleeding with rivaroxaban

Talukdar et al, 2017 – Rivaroxaban versus warfarin

Patients aged ≤65 years, requiring an open operation and who were administered rivaroxaban had a lower incidence of major bleeding when compared to individuals taking warfarin (p-value = 0.020). Patients older than 65 years and undergoing an open operation, had a significant risk for reintervention when given rivaroxaban (p-value = 0.047).

Conclusion: Decrease bleeding risk when administering rivaroxaban. Risk of re-intervention when using rivaroxaban.

COMPASS trial, Eikelboom et al, 2017 – Rivaroxaban + aspirin versus rivaroxaban versus aspirin

The primary outcome of composite CV death, stroke or MI occurred in fewer patients who were administered rivaroxaban and aspirin than patients who were given aspirin only (4.1% compared 5.4%; hazard ratio, 0.76; 95% confidence interval, 0.66 to 0.86; p-value < 0.001). Major bleeding events occurred in more patients who were taking the combination of rivaroxaban and aspirin (3.1% compared to 1.9%; hazard ratio, 1.70; 95% confidence interval, 1.40 to 2.05; p-value < 0.001). A statistically significant difference in intracranial or fatal bleeding events was not observed between the two groups. The primary outcome was comparable for patients in the rivaroxaban group and in the aspirin group. Compared to aspirin only, patients taking rivaroxaban only had more major bleeding events.

Conclusion: Patients taking rivaroxaban and aspirin showed better CV outcomes but had more major bleeding events compared with those taking aspirin only. Treatment with rivaroxaban only did not show better CV outcomes compared to patients on aspirin only, but resulted in major bleeding events.

Subgroup analysis from the COMPASS trial, Anand et al, 2018 – Rivaroxaban versus aspirin

From 6391 patients with lower extremity PAD, 128 patients had an incidence of major adverse limb event (MALE). Following MALE, the one year cumulative risk of a subsequent hospitalization was 95.4%, for vascular amputations the risk was 22.9%, for death the risk was 8.7%, and for major adverse cardiovascular event (MACE) risk was 3.8%. The MALE index event significantly increased the risk of having subsequent hospitalizations (hazard ratio: 7.21; $p < 0.0001$), subsequent amputations (hazard ratio: 197.5; $p < 0.0001$) and death (hazard ratio: 3.23; $p < 0.001$). Compared to aspirin, the combination of rivaroxaban 2.5 mg twice daily and aspirin lowered the incidence of MALE by 43% (p-value = 0.01), total vascular amputations by 58% (p-value = 0.01), peripheral vascular interventions by 24% (p-value = 0.03), and all peripheral vascular outcomes by 24% (p-value = 0.02).

Conclusion: Administration of rivaroxaban 2.5mg twice a day in combination with aspirin, significantly decrease incidence of MALE and related complications.

VOYAGER – PAD, Capell et al, 2018 – Rivaroxaban versus placebo

Ongoing trial – Investigating efficacy of rivaroxaban when used in combination with antiplatelet therapy to decrease major CV and limb ischemic vascular outcomes in high risk PAD patients undergoing peripheral revascularisation.

Table 3.54: Summary of studies showing efficacy and safety outcomes of novel oral anticoagulants when used in peripheral artery disease.

	Study	Efficacy	Safety	Reference
1	Apixaban versus warfarin 884 PAD patients	Similar	Similar	Hu et al, 2017
2	Edoxaban versus warfarin 841 PAD patients	High dose edoxaban shows similar efficacy to warfarin	Similar	Cunningham et al, 2016
3	Edoxaban + aspirin versus clopidogrel + aspirin 203 PAD patients	Lower incidence of restenosis with edoxaban + aspirin	Similar	Moll et al, 2018
4	Rivaroxaban versus warfarin 839 PAD patients	Similar	Higher bleeding risk for rivaroxaban	Jones et al, 2014
5	Rivaroxaban versus warfarin 94 PAD patients	Risk for reintervention with rivaroxaban	Lower major bleeding risk with rivaroxaban	Talukdar et al, 2017
6	Rivaroxaban + aspirin versus rivaroxaban versus aspirin 27,395 patients of which 7470 had PAD	Better CV outcomes with rivaroxaban + aspirin compared to aspirin Similar for rivaroxaban versus aspirin	More major bleeding events with rivaroxaban + aspirin compared to aspirin. More major bleeding events with rivaroxaban compared to aspirin	Eikelboom et al, 2017
7	Rivaroxaban + aspirin versus aspirin 6391 lower extremity PAD	Rivaroxaban + aspirin decreased incidence of MALE, total vascular amputations, peripheral vascular interventions and all peripheral vascular outcomes		Anad et al, 2018

PAD, Peripheral Artery Disease; CV, Cardiovascular; MALE, Major Adverse Limb Events

Studies show that rivaroxaban is the most studied NOAC in PAD. Two from four studies comparing NOACs to warfarin in PAD, showed that NOACs have similar efficacy outcomes to warfarin. Two identified studies show that when added to aspirin, rivaroxaban have favourable efficacy outcomes compared to aspirin alone. Another study showed that when edoxoban was used in combination with aspirin in PAD patients, a lower incidence of restenosis was observed.

3.6 Availability of NOACs on the Maltese market

According to the last version of the hospital formulary (December, 2018), rivaroxaban 10mg tablets are the only NOACs which are available through the national health services for restricted use. Rivaroxaban is reserved for the prevention of venous thromboembolism in patients undergoing elective hip or knee replacement surgery. Treatment is given free of charge for a maximum of fourteen days. NOACs are not available in the out-patients formulary.

Table 3.55 gives an indication of the three NOACs available on the Maltese market together with the cost per tablet in the private sector. Cost of rivaroxaban varies within the national health services according to tender prices.

Table 3.55: Cost of novel oral anticoagulants per tablet

Active Ingredient and dose	Price per tablet (€)
Apixaban 2.5 mg Apixaban 5.0 mg	1.75 1.75[10]
Dabigatran 75mg Dabigatran 110mg Dabigatran 150mg	1.60 1.60 1.57[11]
Rivaroxaban 10mg Rivaroxaban 15mg Rivaroxaban 20mg	3.04 3.04 3.04[12]

[10] Camilleri C. 2018, Personal communication, 29th January 2018
[11] Grima V. 2018, Personal communication, 29th January 2018
[12] Delicata S. 2018, Personal communication, 29th January 2018

Chapter 4

Discussion

4.1 Relevance of the study

The introduction of novel oral anticoagulants (NOACs) into clinical practice provided new alternatives for the management of thromboembolic complications and for thromboprophylaxis. Apart from analysing efficacy of medication, it is essential to assess the safety profile of the drug. A number of studies analysing the safety and efficacy of NOACs in a number of indications have been carried out (Prandoni, 2014; Almutairi et al, 2017; Deitelszweig et al, 2018; Cohen et al, 2018). The study was carried out to analyse and compare commonly reported adverse drug reactions (ADRs) for aspirin and the NOACs; apixaban, dabigatran and rivaroxaban. The study provides a comparative approach between the safety profile for aspirin and the safety profile for NOACs as documented in pharmacovigilance (PV) reports and as reported from a cohort of Maltese patients. A review on the use of NOACs in peripheral artery disease (PAD) was performed to analyse efficacy and safety outcomes of NOACs when used in patients with PAD. The study gives results from a number of studies on the use and possible expansion of indications for NOACs. Patient accessibility to NOACs in the local population was assessed in terms of availability and cost.

The management of thromboembolic complications has always caused challenges in the clinical setting, due to the associated inherent risk of bleeding events which must be counterbalanced with the efficacy of the medication (Ramos-Esquivel, 2015). Selection of medication should be influenced by the patient's risks of thromboembolic and bleeding events and by the specific pharmacokinetic and pharmacodynamics characteristics of antithrombotic medication (Tereschcheno et al, 2016). The introduction of new agents

into the medical scenario provides new therapeutic alternatives which can be better options in areas of practice with unmet needs.

Due to high disease burden related to thromboembolic disease, there is a demand for continued vascular protection, beyond the treatment which is currently available in clinical practice (Bauersachs and Zannad, 2018). As a consequence of an aging population, thromboembolic complications will probably increase, unless the incidence of the disease and complications are minimised by adopting efficacious, economical and widely accessible prophylactic therapy (Hankey et al, 2006). The safety profile of medication should be analysed when choosing medication.

The evolution of specific antidotes for NOACs and the addition of new information and evidence on the efficacy of NOACs in reducing major adverse cardiovascular events (MACE) in patients with health problems such as coronary artery disease (CAD), PAD and heart failure (HF) are essential to help establish new roles for NOACs. The use of NOACs has the potential to expand given that studies prove that NOACs are effective in reducing cardiovascular (CV) events (Weitz, 2015).

This study may help address the evidence gap which exists on the use of NOACs in PAD patients. Studies on post-marketing safety data based on spontaneous ADR reporting are essential for comparing information between different medications.

4.2 Outcomes from pharmacovigilance reports and questionnaires

Differences in the number of reported ADRs for the three NOACs (apixaban, dabigatran and rivaroxaban) and aspirin could have resulted due to differences in the safety profile of the medications, due to differences in consumption trends of medications or due to reporting bias.

The study showed that from the three NOACs analysed, rivaroxaban was the NOAC which had the highest number of reported cases of adverse drug reactions (ADRs) in pharmacovigilance (PV) reports. Apixaban was the NOAC which had the least reported cases of ADRs. The difference in the number of reported cases for the fifteen analysed ADRs for the three NOACs could be attributed to differences in the time when each NOAC was approved for human consumption. From the three investigated NOACs, apixaban was the last NOAC approved for use in the clinical setting.

Differences in the number of reported cases, could be related to the disparity in consumption trends of medication. The finding could be a reflection of prescribing trends for NOACs. Studies show an increase in the prescribing trends for rivaroxaban (Oktay, 2015; Weitz et al, 2015; Castles et al, 2016; Loo et al, 2017). A study by Weitz et al, analysed changes in prescription trends for oral anticoagulant medications between 2008 and 2014, following the introduction of the NOACs in Canada. The study found that there was a decrease in the prescriptions for warfarin for different indications, from 99% in 2010 to 67% in 2014, following availability of NOACs. The use of NOACs increased in patients for different indications. Rivaroxaban was used for venous thromboembolism

(VTE) prevention following major orthopaedic surgery and by 2013, rivaroxaban held a 55% share of the anticoagulant market in orthopaedics. Dabigatran and apixaban together accounted for about 3% of market share for orthopaedics (Weitz et al, 2015).

Another study analysing prescription rates for apixaban, dabigatran, rivaroxaban and warfarin in Australia, between 2010 and 2015, showed that over the five years, prescriptions for NOACs increased more than 100-fold. Rivaroxaban had the highest rise in the number of prescriptions. Between 2012 and 2015, there was a sharp increase in the prescriptions for rivaroxaban (approximately 900,000 prescriptions). A steady increase in prescriptions was seen for apixaban (approximately 300,000 presccriptions) and dabigatran (approximately 300,000). Prescriptions for warfarin remained approximately static until 2013 and then started to decline (Castles et al, 2016).

In a study by Loo et al, the number of patients started on NOACs and warfarin was studied using prescriptions from the United Kingdom from 2009 to 2015. During the study period there was a 31% decrease in the rate of new vitamin K antagonists (VKAs) while the rate of initiation of NOACs increased. A 17-fold increase in initiation of patients on NOACs was seen between the years 2012 and 2015. The study showed that by 2015, NOACs accounted for 56.5% of the oral anticoagulant prescriptions, with rivaroxaban (64.8%) being the most commonly prescribed NOAC, followed by apixaban (29.3%) and dabigatran (5.9%). During the study period, the rate of new dabigatran users was relatively low (approximately 20 patients per 100,000 per year) compared to rivaroxaban and apixaban. For rivaroxaban and apixaban rates of new patients started on the

medications increased to 200.1 for rivaroxaban and to 90.7 for apixaban per 100,000 individuals per year in 2015 (Loo et al, 2017).

The International Medical Statistics (IMS) Healthcare data for global anticoagulation market sales for 2014 showed a 1.35 fold higher usage rate for factor Xa inhibitors when compared to direct thrombin inhibitors. Rivaroxaban was the preferred medication among factor Xa inhibitors as of 2014 (Oktay, 2015).

No patients enrolled for the questionnaire were taking either dabigatran or apixaban. All patients in the NOACs cohort were taking rivaroxaban probably because in Malta, rivaroxaban is the only NOACs which is available for free through the National Health Services. Studies analysing the consumption trends for NOACs in the Maltese population were not available.

An increase in the prescribing of medications causes an increase in the possibility of capturing an ADR following medication intake and hence an increase in reporting of ADRs to PV databases. Information on the safety profile of medications obtained from clinical trials is limited. Additional information on the benefit-risk profile of medication can be obtained from reported ADRs to PV databases (Santoro et al, 2017).

Bleeding-related ADRs were the highest documented ADRs in PV reports and the lowest reported ADRs in patient questionnaires. Reported cases of ADRs from PV reports for aspirin and the NOACs, apixaban, dabigatran and rivaroxaban showed that from the

fifteen ADRs investigated, ADRs associated with bleeding events were the most frequently reported ADRs (N=38,826 reported cases).

Bleeding-related ADRs are the most important ADRs associated with patients taking any type of anticoagulant medication (Van Ryn et al, 2010). Major bleeding is the most important ADR associated with the NOACs. Non-major bleeding risks can occur during use of NOACs, but are usually self-limited (Prisco et al, 2017). Reporting bias results from selective reporting or under-reporting of ADRs to PV databases. Bleeding-related ADRs could possibly be more closely monitored and more freqeuntly reported than other ADRs considered as less important or as less serious relative to bleeding-related ADRs. Medical professionals could possibly be more concerned with bleeding-related ADRs. Selective reporting could be the reason why findings from this study showed that bleeding-related ADRs were the most frequently reported ADRs for all the four medications investigated in the PV database. ADRs reported to PV databases do not reflect the amount of ADRs which actually occur following medication intake. It is estimated that only 10% of all ADRs are actually reported (Biagi et al, 2013). Findings from the study show a bias in the reporting of ADRs to PV databases.

Pairwise comparisons of medication for ADRs showed statistically significant differences between the three NOACs, which could have resulted either due to differences in consumption trends of medications or due to differences in the safety profile of medication. Data from studies comparing the individual safety profiles of NOACs show differences in the safety profiles of the three NOACs (Noseworthy et al, 2016; Almutairi

et al, 2017; Deitelzweig et al, 2018; Cohen et al, 2018). Most of safety profile analysis found in literature, compare NOACs in terms of bleeding risks.

Meta-analyses by Almutairi et al were carried out to analyse the efficacy and safety of NOACs compared to warfarin for patients with atrial fibrillation (AF) and patients with venous thromboembolism (VTE). Results showed that in AF patients, dabigatran, apixaban and edoxaban decreased the risk of haemorrhagic stroke, mortality, major and intracranial haemorrhage by 10% to 71% when compared with VKAs but not rivaroxaban. For patients with VTE, the meta-anlaysis showed inconsistent data between NOACs. Dabigatran, rivaroxaban and apixaban, showed a decreas in the risk of major bleeding when compared to VKAs, with rivaroxaban and edoxaban showing no difference to warfarin with respect to the risk for major bleeding in other studies. The meta-analysis demonstrated that except for dabigatran, NOACs show a reduction of between 61% and 86% in the risk of intracranial haemorrhage and gastrointestinal bleeding of (Almutairi et al, 2017).

In another meta-analysis of eleven studies comparing major bleeding in patients with non-valvular AF, results showed that apixaban was associated with a significant decrease in the risk of major bleeding when compared to warfarin, dabigatran and rivaroxaban. Dabigatran was associated with a significantly lower risk than warfarin and rivaroxaban. A statistically significant difference for major bleeding between rivaroxaban and warfarin was not observed (Deitelzweig et al, 2018).

In a study comparing NOACs and warfarin in patients with AF, results showed that when comparing safety outcomes for bleeding events including any type of bleeding, intracranial bleeding and major bleeding, the annual rates for apixaban and dabigatran were significantly lower compared to warfarin. Warfarin and rivaroxaban had comparable bleeding rates (Larsen et al, 2016). Another study compared the effectiveness and safety of dabigatran, rivaroxaban and apixaban to warfarin in individuals with nonvalvular AF. Results showed that for major bleeding, apixaban (p-value <0.001) and dabigatran (p-value = <0.01) were associated with a lower risk of major bleeding compared to warfarin. Compared to warfarin, rivaroxaban (p-value = 0.60) was associated with a similar risk for major bleeding. For intracranial bleeding, all three NOACs showed a decreased risk when compared to warfarin (Yao et al, 2016). In another study by Noseworthy et al, results showed that in patients with non-valuvular AF, apixaban was associated with a lower risk of major bleeding when compared to dabigatran (p-value <0.001) and to rivaroxaban (p-value <0.001). Rivaroxaban was associated with having an increased risk of major bleeding (p-value <0.01) and intracranial bleeding (p-value <0.05) when compared to dabigatran (Noseworthy et al, 2016).

A study by Cohen et al was carried out with the aim of analysing the evidence on the safety profile of NOACs in AF and VTE management. Analysis was done for different types of bleeding, including major or clinically relevant non-major bleeding, intracranial bleeding and gastrointestinal bleeding. Phase III trials in AF patients showed that NOACs were associated with similar or reduced risks of major or clinically relevant non-major bleeding compared to warfarin. A dose-dependent effect on major bleeding for dabigatran was observed. A statistically lower bleeding rate for dabigatran compared to warfarin was observed for a dose of 110mg twice a day while comparable bleeding rates

for dabigatran 150mg twice daily compared to warfarin were observed. Rivaroxaban was found to have a rate of major bleeding comparable to warfarin, while apixaban compared to warfarin, was associated with a statistically significant reduction in major bleeding. Studies showed that regardless of dose, edoxoban was associated with a significant reduction in all major bleeding compared to warfarin. For VTE, phase III trials for NOACs showed that for clinically relevant non-major bleeding or composite bleeding outcomes, NOACs are at least non-inferior compared to warfarin. For intracranial bleeding, phase III trials showed that in patients with AF and VTE, a significant reduction was observed with dabigatran, rivaroxaban and apixaban compared to warfarin. A meta-analysis of NOACs studies, showed that NOACs have a higher rate of gastrointestinal bleeding than warfarin, with comparable rates of bleeding when using low-dose regimens. Apixaban showed comparable rates of gastrointestinal bleeding with warfarin. High dose edoxaban showed comparable gastrointestinal bleeding rates when compared to warfarin therapy. In patients with VTE, rates of gastrointestinal bleeding for NOACs were similar to warfarin, except for apixaban which showed a statistically significantly lower rate of gastrointestinal bleeding (Cohen et al, 2018).

This study shows statistically significant differences between pairwise comparisons of apixaban, dabigatran and rivaroxaban for all the fifteen ADRs investigated. The finding is consistent with a study by Monaco et al. The study by Monaco et al consisted of a comparative analysis of reported suspected ADRs associated with apixaban, dabigatran and rivaroxaban using the pharmacovigilance database VigiBase. Various differences between the rate and type of ADRs reported to VigiBase, for the three NOACs, were observed (Monaco et al, 2017).

Analysis of literature, showed that when assessing safety and efficacy of NOACs, warfarin is usually used as the common comparator in studies performed for comparative analysis. Aspirin is not usually compared to the NOACs. The study showed that when comparing reported ADRs for aspirin to reported ADRs for rivaroxaban, more ADRs were reported for rivaroxaban. Aspirin is a much older medication which has been used for decades, while rivaroxaban is relatively new, compared to aspirin. The concept of PV did not exist when aspirin was discovered, hence the discrepancy in reporting of ADRs between aspirin and rivaroxaban. Discrepancy between PV reports for aspirin and rivaroxaban could have resulted due to differences in reporting habits from healthcare professionals. ADRs are more likely to be reported for novel medications such as NOACs for which healthcare professionals lack experience, as compared to the more conventional drugs such as aspirin. Information on the safety profile of medications obtained from clinical trials is limited. Additional information on the safety profile of medication can be obtained from reporting of ADRs to PV databases. ADRs related to novel medication are more likely to be reported as this helps generate new information beneficial for clinical practive. When prescribing novel medications, healthcare professionals may be more attentive to ADRs which might cause distress to patients and hence report any new ADR occurring following intake of medication.

When comparing aspirin and rivaroxaban form PV reports, a statistically significant difference was observed between the number of reported ADRs for aspirin and the number of reported ADRs for rivaroxaban for six of the studied ADRs (contusion, dizziness, epistaxis, eye haemorrhage, gingival bleeding and headache). PV reports showed that for both aspirin and rivaroxaban, bleeding-related ADRs were the most frequently reported ADRs. When comparing reported ADRs for aspirin and rivaroxaban

from patient's questionnaire, the number of reported ADRs for the two medications was found to be comparable. As opposed to PV reports, bleeding related ADRs were the least commonly identified ADRs by patients in questionnaires for both aspirin and rivaroxaban. The difference in reporting could have resulted due to a greater inclination to report ADRs to PV databases which are considered as being more serious or more disabling to the patient such as gastrointestinal bleeding rather than reporting ADRs which are considered as minor ADRs or less serious such as gastrointestinal ADRs.

The PV reports analysed for the study were received from a number of different countries around the world. A heterogeneous population increases the robustness of the study as it includes population differences across several countries.

4.3 Studies on novel oral anticoagulants use in peripheral artery disease.

The benefits of using NOACs for various indications have been shown in a number of clinical trials. NOACs have been studied in different patient populations, including acute pulmonary embolism and deep vein thrombosis (DVT), in AF, acute coronary syndrome (ACS) and for the prophylaxis of DVT following knee and hip replacement surgery, as shown in clinical studies (Eriksson et al, 2007; Schulman et al, 2009; Alexander et al, 2011; Connolly et al, 2011; Patel et al, 2011; Buller et al, 2012). There is a paucity of evidence with regards to outcomes for PAD patients treated with NOACs.

This study identified ongoing and completed studies on the use of NOACs for the prevention of thromboembolic complications in PAD patients. Following an extensive literature search eight studies analysing a new therapeutic indication for NOACs in PAD were identified. No studies on the use of dabigatran in PAD patients were identified. The lack of studies on the use of dabigatran in PAD is questionable, since dabigatran is one of the oldest NOACs which was approved for use. The lack of studies on dabigatran use in PAD, may be atttributed to the publishing of a considerable number of safety alerts on dabigatran by regulatory agents and due to the number of studies directed to the safety profile of dabigatran (Motola et al, 2008). The publishing of safety alerts on dabigatran, may have contributed to the paucity of clinical trials on the use of dabigatran in PAD. The majority of identified studies were on rivaroxaban, possibly because rivaroxaban is one of the earliest NOACs which was approved for use.

Studies on the use of NOACs in PAD are limited, which makes it difficult to assess data and identify what is the role of NOACs in PAD patients. The majority of studies which were evaluated compared NOACs to warfarin. Studies comparing aspirin to NOACs in the PAD population would be beneficial to assess the role of NOACs in PAD. Aspirin is indicated for the secondary prevention in PAD (Gerhard-Herman et al, 2016) and hence future studies comparing NOACs and aspirin in PAD could provide important more data on use of NOACs in PAD patients.

Knowledge on the use of NOACs in certain areas of clinical practice such as in PAD is limited. The lack of studies on NOACs, limits the use of NOACs in patient cohorts which are not adequately studied (Connolly and Spyropoulos, 2013). Studies on the use of

NOACs show that NOACs have favourable or comparable outcomes to other antithrombotic medication when used in PAD patients. NOACs could be used as an alternative to other treatment for patients with PAD. With regards to safety outcomes from the identified studies, comparison of NOACs to other antithrombotic medication did not demonstrate that the safety profile of NOACs is superior to the safety profile of other antithrombotic medication when used in PAD patients. More studies on NOACs are necessary to further increase the knowledge on NOACs, which are relatively new to clinical practice.

More data on the safety and efficacy of NOACs would assist healthcare professionals in determining the risk-benefit ratio of therapy for patients. Performing new studies on NOACs will help enhance confidence in the use of such agents and thereby extend the use of NOACs to other patient populations.

The introduction of novel agents into a particular area of practice can contribute to a number of challenges. While it may be clear that NOACs have a potential for use in PAD, incorporation into daily practice may be abated by barriers which inhibit the use of such agents. Barriers include safety concerns such as bleeding, difficulty in identifying patients who will mostly benefit from the medication and cost of medication therapy. Robust evidence-based data is necessary to help in PAD management. Literature lacks trials and data on the management of PAD is sometimes extrapolated from trials done in patients with CAD (Bauersachs and Zannad, 2018). NOACs may provide alternative treatment options in areas of unmet needs such as PAD.

4.4 Accessibility to novel oral anticoagulants in Malta

Three NOACs are authorised to be used in Malta, and rivaroxaban is the only NOAC available for patients through the National Health Service for restricted use probably because rivaroxaban is one of the oldest NOACs and more clinical data is available. Evaluation of the possibility of providing NOACs for other approved indications, which are not on the formulary, would be appropriate especially in patients for whom other treatment options are not effective. Compared to aspirin, the cost of NOACs is still relatively high for the Maltese population, especially for individuals who need the medication for chronic long-term treatment. Cost of NOACs is higher than aspirin due to NOACs being relatively recently approved for use in the clinical scenario (Rose and Bar, 2018).

A cost-effectiveness study in the Maltese population comparing the use of NOACs and aspirin can be conducted in future studies. The cost of medication is not the only aspect which should be considered when analysing the cost-effectiveness of medication. Other aspects which should be considered apart from the estimated drug cost include; financial burden resulting due to thromboembolic events and complications, hospital visits, length of stay in hospital and time that the patient has to stay away from work.

4.5 Limitations

A number of limitations have been identified for the study:

- Postmarketing PV reports are subject to bias such as underreporting and selective reporting of ADRs.

The real number of patients who experience ADRs cannot be identified because of underreporting which can be considerably high (Hazell and Shakir, 2006). It is estimated that only 10% of all ADRs are actually reported (Biagi et al, 2013). There is also a tendency to report ADRs which are considered as serious and which cause considerable harm to the patient.

- Some of the analysed PV reports contained missing data.

Missing information in PV reports affected the analysis of reported cases of ADRs.

- Reporting bias

Given that more patients are prescribed the medication, there is a greater risk that an ADR is identified. The least amount of ADRs were reported for apixaban. Apixaban is the last NOAC which was authorised for use from the three NOACs studied in this research. Aspirin has been used for a longer period of time than NOACs and reporting of ADRs to PV reports did not exist when aspirin started being used. Healthcare professionals may report more ADRs arising from new medications, such as NOACs than ADRs encountered following intake of conventional medications such as aspirin.

- Polypharmacy

Patients included in the study were on other medications and patients may have found it difficult to identify which medication was causing the ADR. Identified ADRs in the patient's questionnaire could have occurred due to intake of other medication and not due to aspirin or rivaroxaban.

- Small sample size and short study period

The small sample size of the patients enrolled for the questionnaire and the short study period could have contributed to the lack of statistical significance between the reported ADRs for aspirin and the reported ADRs for rivaroxaban. The number of patients in Malta who are on NOACs is very limited. Other antithrombotic options are available through the national health services, while rivaroxaban is only available for certain indications. During the study period rivaroxaban was the only NOAC which was identified. Patients on rivaroxaban had been on the medication for a short period of time, and so the study did not capture ADRs which may have occurred following long term use of medication. The majority of patients taking asprin had been on the medication for many years.

- Recall bias

Patients may have not recalled ADRs experienced after the administration of medication. Patients may have found it difficult to identify all ADRs which actually occured following medication administration.

4.6 Recommendations

New studies are necessary to further analyse the safety profile of NOACs. When assessing the efficacy and safety profile of NOACs, warfarin is usually used when carrying comparative analysis. Data from studies comparing NOACs between them, would help in providing useful information about differences in medication profiles. Studies comparing NOACs to aspirin may be conducted. Studies comparing the efficacy and safety of aspirin to NOACs are limited in literature. New information from studies analysing differences between NOACs and aspirin are necessary for managing thromboprophylaxis. Further studies on the use of NOACs in conditions requiring secondary prevention can have an impact on both a local and on an international level. The potential benefit of NOACs in new areas of practice may be assessed.

When assessing spontaneously reported PV reports, the consumption of the medications is rarely used. When carrying out PV studies, it would be appropriate for researchers to take into consideration, and adjust data based on consumption trends of medications (Svendsen et al, 2018). Additional information on consumption trends compared to PV reports would make it easier to interpret data and make results more reliable and robust.

4.7 Conclusions

The introduction of the NOACs into the medical field have caused a change in the management of conditions requiring anticoagulation therapy. A substantial number of clinical trials have been carried out and show that NOACs are usually safe and effective

in different clinical settings (Connolly and Spyropoulos, 2013). The increase in prescription trends for NOACs may be associated with the increase in the number of indications for NOACs (Weitz et al, 2015).

NOACs are becoming accepted as alternative medication which can be used for conditions for which NOACs are approved such as in patients with AF and VTE management. Patient's characteristics need to be evaluated so as to help identify and appropriately manage individual risk factors for bleeding and thrombosis prior to initiating NOAC medication (Cohen et al, 2018).

When prescribing medication for thromboembolic prevention it is important to observe whether there are barriers such as costs and availability which are limiting the use of other antithrombotic medications such as NOACs. Accessibility and availability of medication is important in determining the choice of treatment. Managing well the resources and improving local health policies may ensure that more patients have access to novel medications such as NOACs (Santos and Rosario, 2008).

Establishing tools for individualised treatment decisions for patients may help to rationally choose medication which provides a balance between thrombotic risk and safety concerns such as bleeding, in routine clinical practice (Bauersachs and Zannad, 2018). Differences between the safety profile of aspirin and NOACs, should be cautiously evaluated before choosing the best therapy for the patients. Evaluation may be done on the basis of the patient characteristics, past medical history and concomitant

medications so as to ensure that the most adequate drug is prescribed (Monaco et al, 2017).

Patient accessibility to treatment is an important aspect which should be analysed when considering alternative treatment options. As pharmacists, it is important to strive to improve patient's accessibility to medication and accept the responsibility to assure that ADR reporting is done systematically and consistently for all suspected ADRs (Barry, 2014).

Findings from the study show differences in the reporting of ADRs between aspirin and the three NOACs, apixaban, dabigatran and rivaroxaban. Differences in reporting has been been attributed to a difference in consumption trends between NOACs, reporting bias and probably due to differences between the safety profile of NOACs. Studies have demonstrated that the use of NOACs in PAD patients show favourable efficacy outcomes. Further studies are necessary to identify the role of NOACs in PAD and evaluate the safety outcomes of NOACs when used in PAD. Using NOACs which target other pathways different from the ones targeted by aspirin, may lead to beneficial outcomes for patients with PAD. More data on the safety and efficacy of NOACs is necessary to help in determining the risk-benefit ratio of therapy.

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Appendix 1

L-UNIVERSITÀ TA' MALTA

Msida – Malta
Skola Medika
Sptar Mater Dei

UNIVERSITY OF MALTA

Msida – Malta
Medical School
Mater Dei Hospital

Ref No: **35/2017**

Friday 15th September 2017

Ms. Jessica Attard
'Oliva'
Ghajn Lukin Street
Xaghra, Gozo

Dear Ms. Jessica Attard,

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

Newer oral anticoagulants in peripheral arterial disease

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

Yours sincerely,

Dr. Mario Vassallo
Chairman
Research Ethics Committee

Email: umms@um.edu.mt • ***Web:*** http://www.um.edu.mt/ms

Appendix 2

Patient information sheet

The aim of the study is to compare the use of aspirin to novel oral anticoagulants (NOACs) when used in peripheral artery disease (PAD) treatment. The study will compare the safety and efficacy of aspirin and NOACs. Patients with PAD have a greater risk of having cardiovascular events compared to patients without PAD, therefore, medications to help decrease the risks are necessary. Aspirin is already indicated for the prevention of cardiovascular events in patients with PAD. NOACs are anticoagulants which prevent blood from clotting and therefore prevent risk of stroke and heart attacks

For this study, PAD patients who are currently on aspirin will be chosen to participate in this research study. Furthermore, patients taking the NOACs rivaroxaban, dabigatran and apixaban will also be chosen to participate in the study. The study will be carried out over a two month period. Patients will be divided into two groups; the control group and the experimental group. Those in the control group will include those patients who take aspirin, while patients in the experimental group will include those individuals taking the NOACs. A patient's questionnaire was set up to help collect the necessary information. Patients taking part in the research study will be asked about any adverse drug reactions (ADRs) which might have occurred administration of aspirin or NOACs.

Data from the questionnaire will be collected and evaluated. This data will be compare with data which was obtained from pharmacovigilance reports. The two sets of data will be analysed and inferences drawn out. All patients taking part in the study will be given a code to ensure that all patients remain anonymous.

Informazzjoni għall-pazjent

L-għan ta' dan l-istudju hu li jiġu analizzati d-differenzi bejn il-mediċina asprina u l-antikoagulanti orali ġodda meta jintużaw f'pazjenti li jbatu minn kundizzjoni ta' ċirkulazzjoni ħażina fl-arterji periferali. Pazjenti b'din il-kundizzjoni għandhom riskju akbar li jsoffru minn konsegwenzi kardiovaskulari meta mqabblin ma' pazjenti li ma jbatux minn din il-kundizzjoni, għalhekk huwa tajjeb li jittieħdu medicini li jnaqqsu dawn ir-riskji. L-aspirina hija waħda mill-mediċini li tista' tittieħed biex tnaqqas dawn ir-riskji. L-antikoagulanti orali ġodda jistgħu jistużaw biex jipprevenu li d-demm jgħaqqad u għalhekk tnaqqas ir-riskju ta' puplesija u attakki tal-qalb.

Għal dan l-istudju se jintażgħlu pazjenti li diġa qed jieħdu l-aspirina u li jbatu minn ċirkulazzjoni ħażina fl-arterji periferali. Għal dan l-istudju se jintgħażlu ukoll pazjenti li qed jieħdu l-antikoagulanti orali ġodda, bħal rivaroxaban, dabigatran u apixaban. Dan l-istudju se jsir fuq perjodu ta' xahrejn. Il-pazjenti li se jieħdu sehem se jkunu maqsumin f'żewg gruppi: grupp esperimentiv u l-grupp ta' kontroll. Dawk fil-grupp ta' kontroll se jkunu qed jieħdu l-aspirina tul l-istudju. Dawk fil-grupp esperimentiv se jinkludi pazjenti li jieħdu l-antikoagulanti orali ġodda. Sett ta' mistoqsijiet ġew preparati biex jgħinu tinġabar l-informazzjoni meħtieġa għal dan l–istudju. Il-pazjenti li se jieħdu sehem f'dan l-istudju se jkunu mistoqsija dwar effetti ħżiena li setgħa kellhom wara li ħadu l-aspirina jew antikoagulanti orali ġodda.

L-informazzjoni li se tinġabar mill-mistoqsijiet preparati se tkun miġbura u analizzata. Din l-informazzjoni se tkun ikkomparata ma' informazzjoni miġbura minn rapporti tal-farmakoviġilanza. L-informazzjoni miġbura se tiġu analizzata u ikkomparata flimkien. Kull pazjent se jingħata kodiċi li jassigura li kull pazjent jibqa' anonimu.

Appendix 3

PATIENT INFORMED CONSENT FORM

I, the undersigned, hereby give consent to take part in the research study entitled:

'Newer oral anticoagulants in peripheral arterial disease'

The purpose and details of the study have been explained. I give my consent to the person responsible to this study and her delegates to make the required analyses and observations. The aim of the study is to compare the use of aspirin to novel oral anticoagulants (NOACs) when used as secondary prevention in peripheral artery disease (PAD).

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 express written permission. Patients participating in the study will be given a code in order to ensure anonymity.

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 influence in any way the care and attention and treatment normally given to me.

Should I require further information, I may contact Jessica Attard on 79920922.

Patient's code _____

Name of participant _____

ID no. of participant _____

Signature of participant _____

Name of Chief Investigator _____

ID of Chief Investigator _____

Signature _____

Name of Consultant _____

Date _____

FORMULA TAL-KUNSENS TAL-PAZJENT

Jien, hawn taħt iffirmat/a, nagħti l-kunsens tiegħi biex nieħu sehem fi studju riċerka bl-isem ta':

'L-użu ta' antikoagulanti orali ġodda fil-kundizzjoni ta' ċirkulazzjoni ħażina fl-arterji periferali'

L-għan u d-dettalji ta' l-istudju ġew spejgati lili. Nagħti l-kunsens tiegħi lill-persuna responsabbli għal din ir-riċerka u l-assistenti tagħha biex jagħmlu l-analażi u l-osservazjonijiet li hemm bżonn għal dan l-istudju. L-għan ta' dan l-istudju hu li janalizza d-differenzi bejn il-mediċina asprina u l-antikoagulanti orali ġodda meta jintużaw għall-prevenzjoni sekondarja f'pazjenti li jbatu minn kundizzjoni ta' ċirkulazzjoni ħażina fl-arterji periferali.

Jiena nifhem li r-riżultati ta' dan l-istudju jistgħu jintużaw għal skopijiet xjentifiċi u jista' jiġi ppubblikat f'ġurnali jew artikli xjentifiċi. Jekk isir hekk b'ebda mod ma nista' nkun identifikat/a, individwalment jew bħala parti minn grupp, mingħajr il-kunsens tiegħi bil-miktub. Kull pazjent se jingħata kodiċi biex jiġi assigurat li kull informazzjoni li tingħata tibqa anonima.

Jiena ma għandi l-ebda dmir li nieħu sehem f'dan l-istudju u dan qed nagħmlu b'mod volontarju. 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.

Jekk ikolli xi diffikulta' waqt l-istudju, nista' nikkuntattja lil Jessica Attard fuq in-numru 79920922.

Kodiċi tal-pazjent _____

Isem tal-partiċipant _____

Numru ta' l-identita' _____

Firma tal-partiċipant _____

Isem tal-persuna responsabbli għal din ir-riċerka _____

Numru ta' l-identita' _____

Firma _____

Isem tal-Konsulent _____

Data' _____

Appendix 4

Patient profile form

Patient Code _____ Date _____

1) Demographic data

Age _____ Gender M F

2) Smoking Status

a) Non-smoker _____

b) Smoker _____ No. of cigarettes per day _____

c) Previous smoker_____

Smoking years _____ No. of cigarettes per day _____ When did patient stop _____ _

3) Amount of physical activity per week

0 - ½ hr _____ ½ - 1hr _____ 1hr - 2½ hr _____ More than 2½ hr_____ ___

4) Past Medical History

Diabetes _____ Hypertension_____ Hypercholesterolemia _____ ___

Others:	

5) Medication history

Active ingredient and dosage strength	**Dosage regimen**

6) Allergies

No _____ Yes _____

7a) Previous cardiovascular event

Ischaemic Heart Disease including Myocardial Infarction or need for PCI/CABG

Cerebrovascular Accident

Transient Ischaemic Attack

b) Did this occur while the patient was on aspirin or NOACs? _____

Questions on aspirin/NOACs

8) Patient is on: Aspirin _____ NOAC _____

9) How long has the patient been on aspirin/NOACs?

0 - 5 years_____ 5 – 10 years _____ 10 – 15 years _____ More than 15 years _ _____

10a) Did the patient encounter any adverse drug reaction (ADR) after starting aspirin or NOACs?

No _____ Yes _____

Table 1: Classification for severity of adverse drug reations.*

Severity	
Mild	Bothersome, requiring no change in therapy, no medical attention
Moderate	Needs change in therapy, additional treatment, dangerous, serious , worrisome, requires hospitalisation
Severe	Disabling, life-threatening

Adverse drug reaction	**Severity***		
	Mild	Moderate	Severe
Hypotension			
Gingival bleeding			
Gastro-intestinal haemorrhage			
Gastro-intestinal and abdominal pains			
Epistaxis			
Eye Haemorrhage			
Bruising			
Dyspepsia			
Nausea			
Vomiting			
Diarrhoea			
Constipation			
Dizziness			
Headache			

Other ADRs: _____

_____

b) If yes, what action was taken?

_____

_____

c) When did the ADR occur?

After 1st dose _____ During the 1st month _____

During the 1st year _____ After the 1st year _____

11) Does the patient know why aspirin/NOACs was prescribed?

Yes _____ No_____

Reason given by patient: _____

_

12) According to the patient, is it safe to take anti-inflammatory medicines like ibuprofen and diclofenac while taking aspirin or NOACs?

Yes _____ No _____ Don't know _____

13) Does the patient feel worried about getting ADRs after taking aspirin/NOACs?

Never	Rarely	Sometimes	Almost Always	Always
1	2	3	4	5

14) Does the patient feel worried of having complications such as stroke or myocardial infarction if aspirin/NOACs is not taken?

Never	Rarely	Sometimes	Almost Always	Always
1	2	3	4	5

15)Would the patient inform a surgeon, dentist or other health professional that he/she takes aspirin or NOACs before undergoing surgery or a procedure?

Yes _____ No _____ Don't know _____

Any comments:

_____
_____

Profil tal-pazjent

Kodiċi tal-pazjent _____ Data' _____

1) Informazzjoni demografika

Eta' _____ Ġeneru M F

2) Informazzjoni rigward tipjip

a) Qatt ma pejjep _____

b) Ipejjep _____ Numru ta' sigaretti fil-ġurnata _____

ċ) Kien ipejjep _____ Snin ta'tipjip _____ Numru ta' sigaretti fil-ġurnata _____

Kemm-il sena ilu li l-pazjent waqaf ipejjep _____

3) Frekwenza ta' Attivita' fiżika fil-gimgħa

0 – 30 minuta _____ 30 - 60 minuta _____ 60 – 150-il minuta _____

Aktar minn 150-il minuta _____

4) Storja Medika

Dijabete _____ Pressjoni għolja _____ Kolesterol għoli fid-demm _____

Oħrajn:	

5) Mediċini li juża' l-pazjent

Prinċipju attiv u doża	**Reġimen ta' dożaġġ**

6) Allerġiji

Le _____ Iva _____

7a)Avventimenti kardjovaskolari li l-pazjent għadda minnhom

Mard iskemiku tal-qalb li jinkludi attakk tal-qalb jew bżonn ta' PCI/CABG

Puplesija

Riħ ta' puplesija

b) Il-pazjent kien fuq l-aspirina jew l-antikoagulanti orali ġodda meta ġara dan?

_____

Mistoqsijiet fuq l-aspirina/ antikoagulanti orali ġodda

8) Il-Pazjent qiegħed fuq :

aspirina _____ antikoagulanti orali ġodda _____

9) Kemm ilu l-pazjent fuq l-aspirina jew l-antikoagulanti orali ġodda?

0 – 5 snin ____ 5 – 10 snin _____

10 – 15-il sena _____ Aktar minn 15-il sena _____

10a) Min mindu beda l-mediċina, l-pazjent iltaqa' ma' xi effett mhux mixtieq?

Le _____ Iva _____

Tabella 1: Klassifikazzjoni tal-effetti mhux mixtieqa.*

Severita'	
Ħafif	Kemmxejn iddejqek, m'hemmx bżonn tbiddel il-mediċina, m'hem mx bżonn attenzjoni medika
Moderat	Hemm bżonn ta' tibdil fil-mediċina jew iżżid mediċina, perikoluż , serju, inkwetanti, bżonn li l-pazjent jidħol l-isptar
Severa	Ta' theddida għall-ħajja

Effett mhux mixtieq	Severita’		
	Ħafif	**Moderat**	**Severa**
Pressjoni Baxxa			
Ħanek jinfasad			
Emorraġija gastrointestinali			
Uġigħ Gastrointestinali u addominali			
Tinfaraġ			
Emorraġija fl-għajnejn			
Tbenġil			
Dispepsja			
Dardir			
Tirremetti			
Dijarea			
Stitikezza			
Sturdament			
Uġigħ ta’ ras			

Effetti mhux mixtieq oħrajn

_____

_____

b) Jekk iva, x’azzjoni ittieħdet?

_____

_____

ċ) Meta ġara l-effett mhux mixtieq?

Wara l-ewwel doża _____ Fl-ewwel xahar _____

Fl-ewwel sena _____ Wara l-ewwel sena _____

11) Il-pazjent jaf għalfejn tittieħet l-aspirina jew l-antikoagulanti orali ġodda?

Iva _____ Le_____

Raġuni li ta’ l-pazjent:

_____

12) Skond il-pazjent, hemm xi riskji jekk jittieħdu mediċini anti-infjammatorji bħal ibuprofen u diclofenac mal-aspirina jew l-antikoagulanti orali ġodda?

Iva _____ Le_____ Ma nafx _____

13) Il-pazjent jinkwieta li jkollu xi effett mhux mixtieq wara li jieħu l-aspirina jew l-antikoagulanti orali ġodda?

Qatt	Rari	Xi drabi	Kważi dejjem	Dejjem
1	2	3	4	5

14) Il-pazjent jinkwieta li jista' jkollu xi kumplikazzjonijiet bħal puplesija jew attakk tal-qalb jekk ma jieħux l-aspirina jew l-antikoagulanti orali ġodda?

Qatt	Rari	Xi drabi	Kważi dejjem	Dejjem
1	2	3	4	5

15) Jekk il-pazjent ikun se jagħmel xi operazzjoni jew xi proċedura oħra, jinforma lil kirurku, dentist jew lil xi professjonist ieħor li qed jieħu l-aspirina jew l-antikoagulanti orali ġodda?

Iva _____ Le _____ Ma nafx _____

Xi kummenti oħra:

_____

_____

Appendix 5

Tukey Post Hoc Test for Abdominal Pain

Tukey Post Hoc Test - Abdominal Pain

(I) Medication	(J) Medication	Mean Difference (I-J)	Std. Error	P-value
Aspirin	Apixaban	52.200	9.142	0.000
	Debigatran	13.400	9.142	0.480
	Rivaroxaban	-12.600	9.142	0.530
Apixaban	Aspirin	-52.200	9.142	0.000
	Debigatran	-38.800	9.142	0.003
	Rivaroxaban	-64.800	9.142	0.000
Debigatran	Aspirin	-13.400	9.142	0.480
	Apixaban	38.800	9.142	0.003
	Rivaroxaban	-26.000	9.142	0.052
Rivaroxaban	Aspirin	12.600	9.142	0.530
	Apixaban	64.800	9.142	0.000
	Debigatran	26.000	9.142	0.052

Tukey Post Hoc Test for Constipation

Tukey Post Hoc Test - Constipation

(I) Medication	(J) Medication	Mean Difference (I-J)	Std. Error	P-value
Aspirin	Apixaban	9.200	6.398	0.495
	Dabigatran	9.200	6.398	0.495
	Rivaroxaban	-17.000	6.398	0.074
Apixaban	Aspirin	-9.200	6.398	0.495
	Dabigatran	0.000	6.398	1.000
	Rivaroxaban	-26.200	6.398	0.004
Dabigatran	Aspirin	-9.200	6.398	0.495
	Apixaban	0.000	6.398	1.000
	Rivaroxaban	-26.200	6.398	0.004
Rivaroxaban	Aspirin	17.000	6.398	0.074
	Apixaban	26.200	6.398	0.004
	Dabigatran	26.200	6.398	0.004

Tukey Post Hoc Test for Contusion

Tukey Post Hoc Test - Contusion

	(J) Medication	Mean Difference (I-J)	Std. Error	P-value
Aspirin	Apixaban	5.800	28.949	0.997
	Dabigatran	-.600	28.949	1.000
	Rivaroxaban	-148.400	28.949	0.001
Apixaban	Aspirin	-5.800	28.949	0.997
	Dabigatran	-6.400	28.949	0.996
	Rivaroxaban	-154.200	28.949	0.000
Dabigatran	Aspirin	0.600	28.949	1.000
	Apixaban	6.400	28.949	0.996
	Rivaroxaban	-147.800	28.949	0.001
Rivaroxaban	Aspirin	148.400	28.949	0.001
	Apixaban	154.200	28.949	0.000
	Dabigatran	147.800	28.949	0.001

Tukey Post Hoc Test for Diarrhoea

Tukey Post Hoc Test - Diarrhoea

(I) Medication	(J) Medication	Mean Difference (I-J)	Std. Error	P-value
Aspirin	Apixaban	25.000	14.481	0.343
	Dabigatran	-14.000	14.481	0.770
	Rivaroxaban	-34.800	14.481	0.117
Apixaban	Aspirin	-25.000	14.481	0.343
	Dabigatran	-39.000	14.481	0.069
	Rivaroxaban	-59.800*	14.481	0.004
Dabigatran	Aspirin	14.000	14.481	0.770
	Apixaban	39.000	14.481	0.069
	Rivaroxaban	-20.800	14.481	0.496
Rivaroxaban	Aspirin	34.800	14.481	0.117
	Apixaban	59.800*	14.481	0.004
	Dabigatran	20.800	14.481	0.496

Tukey Post Hoc Test for Dizziness

Tukey Post Hoc Test - Dizziness

(I) Medication	(J) Medication	Mean Difference (I-J)	Std. Error	P-value
Aspirin	Apixaban	25.000	27.033	0.792
	Dabigatran	41.000	27.033	0.451
	Rivaroxaban	-130.400	27.033	0.001
Apixaban	Aspirin	-25.000	27.033	0.792
	Dabigatran	16.000	27.033	0.933
	Rivaroxaban	-155.400	27.033	0.000
Dabigatran	Aspirin	-41.000	27.033	0.451
	Apixaban	-16.000	27.033	0.933
	Rivaroxaban	-171.400	27.033	0.000
Rivaroxaban	Aspirin	130.400	27.033	0.001
	Apixaban	155.400	27.033	0.000
	Dabigatran	171.400	27.033	0.000

Tukey Post Hoc Test for Dyspepsia

Tukey Post Hoc Test - Dyspepsia

(I) Medication	(J) Medication	Mean Difference (I-J)	Std. Error	P-value
Aspirin	Apixaban	22.800	10.452	0.171
	Dabigatran	-70.400	10.452	0.000
	Rivaroxaban	5.000	10.452	0.963
Apixaban	Aspirin	-22.800	10.452	0.171
	Dabigatran	-93.200	10.452	0.000
	Rivaroxaban	-17.800	10.452	0.354
Dabigatran	Aspirin	70.400	10.452	0.000
	Apixaban	93.200	10.452	0.000
	Rivaroxaban	75.400	10.452	0.000
Rivaroxaban	Aspirin	-5.000	10.452	0.963
	Apixaban	17.800	10.452	0.354
	Dabigatran	-75.400	10.452	0.000

Tukey Post Hoc Test for Epistaxsis

Tukey Post Hoc Test - Epistaxis

(I) Medication	(J) Medication	Mean Difference (I-J)	Std. Error	P-value
Aspirin	Apixaban	414.600	107.508	0.007
	Dabigatran	431.600	107.508	0.005
	Rivaroxaban	-310.200	107.508	0.048
Apixaban	Aspirin	-414.600	107.508	0.007
	Dabigatran	17.000	107.508	0.999
	Rivaroxaban	-724.800	107.508	0.000
Dabigatran	Aspirin	-431.600	107.508	0.005
	Apixaban	-17.000	107.508	0.999
	Rivaroxaban	-741.800	107.508	0.000
Rivaroxaban	Aspirin	310.200	107.508	0.048
	Apixaban	724.800	107.508	0.000
	Dabigatran	741.800	107.508	0.000

Tukey Post Hoc Test for Eye-haemorrhage

Tukey Post Hoc Test - Eye haemorrhage

(I) Medication	(J) Medication	Mean Difference (I-J)	Std. Error	Sig.
Aspirin	Apixaban	-8.000	9.506	0.834
	Dabigatran	11.800	9.506	0.611
	Rivaroxaban	-69.400	9.506	0.000
Apixaban	Aspirin	8.000	9.506	0.834
	Dabigatran	19.800	9.506	0.201
	Rivaroxaban	-61.400	9.506	0.000
Dabigatran	Aspirin	-11.800	9.506	0.611
	Apixaban	-19.800	9.506	0.201
	Rivaroxaban	-81.200	9.506	0.000
Rivaroxaban	Aspirin	69.400	9.506	0.000
	Apixaban	61.400	9.506	0.000
	Dabigatran	81.200	9.506	0.000

Tukey Post Hoc Test for Gastrointestinal bleeding

Tukey Post Hoc Test - GI bleeding

(I) Medication	(J) Medication	Mean Difference (I-J)	Std. Error	P-value
Aspirin	Apixaban	822.600	602.182	0.537
	Dabigatran	106.800	602.182	0.998
	Rivaroxaban	-1423.800	602.182	0.125
Apixaban	Aspirin	-822.600	602.182	0.537
	Dabigatran	-715.800	602.182	0.642
	Rivaroxaban	-2246.400	602.182	0.009
Dabigatran	Aspirin	-106.800	602.182	0.998
	Apixaban	715.800	602.182	0.642
	Rivaroxaban	-1530.600	602.182	0.091
Rivaroxaban	Aspirin	1423.800	602.182	0.125
	Apixaban	2246.400	602.182	0.009
	Dabigatran	1530.600	602.182	0.091

Tukey Post Hoc Test for Gingival bleeding

Tukey Post Hoc Test - Gingival bleeding

(I) Medication	(J) Medication	Mean Difference (I-J)	Std. Error	P-value
Aspirin	Apixaban	27.400	18.740	0.482
	Dabigatran	25.000	18.740	0.556
	Rivaroxaban	-111.200	18.740	0.000
Apixaban	Aspirin	-27.400	18.740	0.482
	Dabigatran	-2.400	18.740	0.999
	Rivaroxaban	-138.600	18.740	0.000
Dabigatran	Aspirin	-25.000	18.740	0.556
	Apixaban	2.400	18.740	0.999
	Rivaroxaban	-136.200	18.740	0.000
Rivaroxaban	Aspirin	111.200	18.740	0.000
	Apixaban	138.600	18.740	0.000
	Dabigatran	136.200	18.740	0.000

Tukey Post Hoc Test for Gastrointestinal pain

Tukey Post Hoc Test - GI pain

(I) Medication	(J) Medication	Mean Difference (I-J)	Std. Error	P-value
Aspirin	Apixaban	4.200	1.277	0.022
	Dabigatran	3.800	1.277	0.040
	Rivaroxaban	3.400	1.277	0.073
Apixaban	Aspirin	-4.200	1.277	0.022
	Dabigatran	-.400	1.277	0.989
	Rivaroxaban	-.800	1.277	0.922
Dabigatran	Aspirin	-3.800	1.277	0.040
	Apixaban	0.400	1.277	0.989
	Rivaroxaban	-.400	1.277	0.989
Rivaroxaban	Aspirin	-3.400	1.277	0.073
	Apixaban	0.800	1.277	0.922
	Dabigatran	0.400	1.277	0.989

Tukey Post Hoc Test for Headache

Tukey Post Hoc Test - Headache

(I) Medication	(J) Medication	Mean Difference (I-J)	Std. Error	P-value
Aspirin	Apixaban	33.800	20.193	0.369
	Dabigatran	35.000	20.193	0.340
	Rivaroxaban	-116.800	20.193	0.000
Apixaban	Aspirin	-33.800	20.193	0.369
	Dabigatran	1.200	20.193	1.000
	Rivaroxaban	-150.600	20.193	0.000
Dabigatran	Aspirin	-35.000	20.193	0.340
	Apixaban	-1.200	20.193	1.000
	Rivaroxaban	-151.800	20.193	0.000
Rivaroxaban	Aspirin	116.800	20.193	0.000
	Apixaban	150.600	20.193	0.000
	Dabigatran	151.800	20.193	0.000

Tukey Post Hoc Test for Hypotension

Tukey Post Hoc Test - Hypotension

(I) Medication	(J) Medication	Mean Difference (I-J)	Std. Error	P-value
Aspirin	Apixaban	41.000	22.369	0.295
	Dabigatran	-11.200	22.369	0.958
	Rivaroxaban	-23.200	22.369	0.731
Apixaban	Aspirin	-41.000	22.369	0.295
	Dabigatran	-52.200	22.369	0.132
	Rivaroxaban	-64.200	22.369	0.049
Dabigatran	Aspirin	11.200	22.369	0.958
	Apixaban	52.200	22.369	0.132
	Rivaroxaban	-12.000	22.369	0.949
Rivaroxaban	Aspirin	23.200	22.369	0.731
	Apixaban	64.200	22.369	0.049
	Dabigatran	12.000	22.369	0.949

Tukey Post Hoc Test for Nausea

Tukey Post Hoc Test - Nausea

(I) Medication	(J) Medication	Mean Difference (I-J)	Std. Error	P-value
Aspirin	Apixaban	53.000	17.053	0.031
	Dabigatran	32.800	17.053	0.258
	Rivaroxaban	-48.400	17.053	0.052
Apixaban	Aspirin	-53.000	17.053	0.031
	Dabigatran	-20.200	17.053	0.645
	Rivaroxaban	-101.400	17.053	0.000
Dabigatran	Aspirin	-32.800	17.053	0.258
	Apixaban	20.200	17.053	0.645
	Rivaroxaban	-81.200	17.053	0.001
Rivaroxaban	Aspirin	48.400	17.053	0.052
	Apixaban	101.400	17.053	0.000
	Dabigatran	81.200	17.053	0.001

Tukey Post Hoc Test for Vomiting

Tukey Post Hoc Test - Vomiting

(I) Medication	(J) Medication	Mean Difference (I-J)	Std. Error	P-value
Aspirin	Apixaban	82.600	13.574	0.000
	Dabigatran	57.600	13.574	0.003
	Rivaroxaban	3.000	13.574	0.996
Apixaban	Aspirin	-82.600	13.574	0.000
	Dabigatran	-25.000	13.574	0.291
	Rivaroxaban	-79.600	13.574	0.000
Dabigatran	Aspirin	-57.600	13.574	0.003
	Apixaban	25.000	13.574	0.291
	Rivaroxaban	-54.600	13.574	0.005
Rivaroxaban	Aspirin	-3.000	13.574	0.996
	Apixaban	79.600	13.574	0.000
	Dabigatran	54.600	13.574	0.005

P-values which are less than the 0.05 level of significance show that there is statistically significant difference between the reported ADR and two medication pairs.

Appendix 6

Studies on the use of NOACs in PAD.

Study	Study Description	Study Design	Intervention	Results	Comments
Jones et al, 2014	To identify the absolute rates of CVA and bleeding events and the efficacy and safety of rivaroxaban compared to warfarin in patients with and without PAD.	14264 patients were enrolled from 45 countries from 1178 centres for the ROCKET AF study. From these, 839 patients had concomitant PAD and AF and were included for a *post hoc* analysis.	• Rivaroxaban 20mg daily or 15mg daily in patients with CrCl 30-49 mL/min • Warfarin – dose adjusted according to INR	Efficacy of rivaroxaban and warfarin on primary outcome was comparable in patients with and without PAD. PAD patients who were administered rivaroxaban had a greater relative risk of major or non-major clinically relevant bleeding when compared to warfarin.	A *post hoc* and subgroup analysis of patients recruited for the ROCKET AF study and who were diagnosed with PAD.
Cunningham et al, 2016	To compare the use of edoxaban and warfarin in patients with AF and concomitant PAD. The primary efficacy and safety endpoint were stroke or systemic embolism and major bleeding.	21,105 patients from the ENGAGE AF-TIMI 48 were randomised to either warfarin, low dose edoxaban and high dose edoxaban. A total of 841 (4%) of patients had concomitant PAD.	• Warfarin – dose adjusted according to INR • High dose edoxaban 60/30mg • Low dose edoxoban 30/15mg	In individuals with PAD, rates of stroke, systemic embolism and major bleeding were comparable for high dose edoxaban and warfarin. Patients on low dose edoxaban had higher rates of stroke or systemic	

				embolism compared to warfarin. Significant reductions in CV deaths and intracranial haemorrhage with high dose edoxaban were also observed both in patients with or without PAD.	
COMPASS (Eikelboom et al, 2017; ClinicalTrials.gov Identifier: NCT01776424)	To evaluate the combination of rivaroxaban and aspirin, to rivaroxaban alone, to aspirin alone in the secondary prevention of major CV events including MI, stroke or CV deaths in patients having stable CAD and PAD	Double-blind 27,395 patients were recruited from 33 countries at 602 centres Patients had a history of stable atherosclerotic vascular disease – CAD, PAD or both. 7470 patients had PAD.	• Rivaroxaban 2.5mg twice daily + aspirin 100mg daily • Rivaroxaban 5mg daily • Aspirin 100mg daily	Low dose rivaroxaban in combination with aspirin decreased major adverse CV and limb events when compared to aspirin alone. Risk of major bleeding events was increased, but fatal or critical organ bleeding was not. Patients treated with rivaroxaban only did not show better CV related outcomes than aspirin alone.	The study was stopped during Phase 3 due to the positive outcomes attained. Rivaroxaban-plus-aspirin group showed superiority versus standard of care and study was stopped after a mean follow-up of 23 months.

Hu et al, 2017	To assess the efficacy and safety of apixaban when compared to warfarin in AF patients with or without PAD.	A total of 18201 patients were recruited for the ARISTOTLE trial and from these 884 patients had PAD at baseline and were included for a subgroup analysis.	• Apixaban 5mg twice daily • Warfarin – dose adjusted according to INR	The risk of having a stroke or systemic embolism was comparable in patients with or without PAD and who were on either apixaban or warfarin. PAD patients did not have a statistically significant decrease in major or clinically relevant non-major bleeding with apixaban when compared to patients on warfarin	From all the patients enrolled for the ARISTOTLE trial, only a relatively small proportion (4.9%) of patients were identified to have PAD at baseline. The lack of statistical significance in reduction of major or clinically relevant non-major bleeding could have resulted due to the small sample size of patients with PAD compared to a larger population without PAD.
Talukdar et al, 2017	To analyse the safety and efficacy of rivaroxaban when compared to warfarin in individuals performing peripheral arterial interventions	Patient were administered rivaroxaban or warfarin following a peripheral artery procedure; 44 patients were on rivaroxaban and 50 patients were	• Rivaroxaban • Warfarin	Patients aged ≤65 years, requiring an open operation and who were administered rivaroxaban had a lower incidence of major bleeding when compared to individuals taking	

		administered warfarin.		warfarin. Patients older than 65 years and undergoing an open operation, had a significant risk for re interventon when given rivaroxaban.	
ePAD (Tangelder et al, 2015; Moll et al,2018; ClinicalTrials.gov Identifier: NCT01802775)	To analyse the safety and efficacy of adding edoxaban to aspirin in PAD patients following femoropopliteal endovascular intervention with or without stent placement when compared to patients to patients on clopidogrel and aspirin.	Open label study 203 participants from 7 countries Primary safety endpoint – major or clinically relevant non-major bleeding Primary efficacy endpoint – restenosis or reocclusion	• Edoxoban 60mg daily + aspirin 100mg daily • Clopidogrel 75mg daily + aspirin100mg daily	In PAD patients who undergo revascularisation procedures the risk of major or life threatening bleeding is similar in patients on edoxaban and aspirin compared to patients on clopidogrel and aspirin. The risk of restenosis or reocclusion was lower for patients with edoxaban and aspirin.	Edoxoban and clopidogrel were administered for 3 months while aspirin was administered for 6 months. A more adequately sized study is necessary to confirm findings from the study.
Subgroup analysis from COMPASS trial (Anand et al, 2018)	Patients with lower extremity PAD have a greater risk of having major adverse cardiovascular	Double blind study 6391 patients having lower extremity PAD and who were	• Rivaroxaban 2.5mg twice daily + aspirin 100mg daily	A total of 128 PAD patients suffered an episode of MALE. The risk of subsequent hospitalisation was	Subgroup analysis of patients from the COMPASS trial.

	events (MACE) and major adverse limb events (MALE). To analyse weather hospitalisations, MACE, amputations and deaths were higher after first episode of MALE when compared to PAD patients who do not suffer from MALE. To analyse the impact of medication on the incidence of MALE, peripheral vascular interventions and peripheral vascular outcomes.	enrolled in the COMPASS trial MALE was defined as patients having severe limb ischemia and required an intervention or major vascular amputation.	• Rivaroxaban 5mg daily • Aspirin 100mg daily	95.4%, for subsequent vascular amputations the risk was 22.9%, for death 8.7% and for MACE 3.8%. Compared to aspirin alone, the combination of rivaroxaban 2.5 mg twice daily and aspirin decreased the incidence of MALE by 43%, vascular amputations by 58% peripheral vascular interventions by 24% and all peripheral vascular outcomes by 24%.	
VOYAGER – PAD (Capell et al, 2018; ClinicalTrials.gov Identifier: NCT02504216)	To evaluate whether rivaroxaban in combination with standard of care treatment, decreases the risk of major thrombotic vascular events in patients with symptomatic	Double-blind Multicenter study including 6536 participants Clinical events evaluated include complications related	• Rivaroxaban 2.5mg twice daily • Placebo twice daily	Results not published.	Study is still ongoing and estimated completion date is in early 2019.

	PAD who undergo peripheral revasculisation procedures in the lower extremities when compared to placebo.	to the heart and brain (MI, CVA and CV death) and legs (acute limb ischemia and major amputation)			

CVA, Cerebrovascular Accident; PAD, Peripheral Artery Disease; ROCKET-AF, An Efficacy and Safety Study of Rivaroxaban With Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Patients With Nonvalvular Atrial Fibrillation; AF, Atrial Fibrillation; CrCL, Creatinine Clearance; INR, International Normalized Ratio; ENGAGE AF-TIMI 48, Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48; COMPASS, Cardiovascular Outcomes for People Using Anticoagulation Strategies; CV, Cardiovascular; MI, Myocardial Infarction; CAD, Coronary Artery Disease; ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; ePAD, Edoxaban in Peripheral Arterial Disease; MACE, Major Adverse Cardiac Events; MALE, Major Adverse Limb Events; VOYAGER-PAD, Vascular Outcomes study of acetylsalicylic acid along with rivaroxaban in endovascular or surgical limb revascularization for peripheral artery disease

Appendix 7

X Malta Medical School Conference Abstract

Aspirin and novel oral anticoagulants: Reporting of adverse drug reactions.

Jessica Attard, Janis Vella Szijj, Anthony Serracino Inglott

Introduction

The use of novel oral anticoagulants (NOACs) clinically provided alternative options for thromboprophylaxis.

Methods

Pharmacovigilance (PV) reports from Eudravigilance between 2013-2017, compared fifteen adverse drug reactions (ADRs) for aspirin and NOACs (apixaban, dabigatran and rivaroxaban). A questionnaire was developed to collect information on ADRs encountered by patients while taking aspirin or NOACs. Fifty patients were recruited (aspirin=25, rivaroxaban=25). Documented ADRs from PV reports were compared to reported ADRs from patients. A literature search identified studies on the off-label use of NOACs in peripheral artery disease (PAD).

Results

Bleeding-related ADRs (38,826/51,391) were the highest reported in PV reports. Gastrointestinal bleeding (n=25,892) was the commonest reported ADR for aspirin(n=5,855), apixaban(n=1,742), dabigatran(n=5,321), and rivaroxaban(n=12,974). Reported ADRs were highest for rivaroxaban(n=24,832). Statistically significant differences were observed for reported ADRs in reports. Thirty-six recruited patients had

at least one ADR (aspirin=18, rivaroxaban=18). Bleeding-related ADRs were least reported (aspirin=11, rivaroxaban=4) in questionnaires. Eight studies analysing NOACs use in PAD were identified.

Conclusions

Bleeding-related ADRs were highest in PV and lowest in questionnaires, suggestive of under-reporting of ADRs considered to be minor. High numbers of reported ADRs for rivaroxaban compared to dabigatran and apixaban, possibly reflect consumption trends. Differences in safety profiles and reporting bias might account for differences in reported ADRs. ADRs are more likely to be reported for novel medications compared to conventional drugs. Two studies on PAD showed that when added to aspirin, NOACs demonstrated favourable efficacy compared to aspirin alone. Further studies analysing safety and efficacy of NOACs will provide additional data on the risk-benefit profile.

European Association of Hospital Pharmacist Congress Abstract

Aspirin and novel oral anticoagulants: Reporting of adverse drug reactions.

Jessica Attard, Janis Vella Szijj, Anthony Serracino Inglott

Background

The novel oral anticoagulants (NOACs) provided alternative options for thromboprophylaxis. The efficacy of conventional antithrombotic medications such as aspirin may vary between patients and alternative medications need to be identified.

Purpose

To carry out comparative analysis of adverse drug reactions (ADRs) reported for aspirin and NOACs. To identify studies on the use of NOACs in peripheral artery disease (PAD).

Materials and Methods

Pharmacovigilance (PV) reports from Eudravigilance between 2013 and 2017 compared fifteen ADRs for aspirin and NOACs (apixaban, dabigatran and rivaroxaban). A questionnaire was developed to collect information on ADRs encountered by patients while taking aspirin or NOACs. Fifty patients were recruited (25-on aspirin, 25-on rivaroxaban). Documented ADRs from PV reports were compared to reported ADRs from patients. A literature search was performed to identify studies on the off-label use of NOACs in PAD.

Results

Bleeding-related ADRs (38,826/51,391) were the commonest reported ADRs in PV reports. Gastrointestinal bleeding (n=25,892) was the most frequently reported ADR for

aspirin (n=5,855), apixaban (n=1,742), dabigatran (n=5,321), and rivaroxaban (n=12,974). Reported ADRs were highest for rivaroxaban (n=24,832). For all fifteen ADRs investigated, statistically significant differences were observed between the four medications when comparing reported cases of ADRs. Thirty-six recruited patients had at least one ADR (aspirin=18, rivaroxaban=18). Bleeding-related ADRs were the least reported (aspirin=11, rivaroxaban=4) in questionnaires. Eight studies analysing the use of NOACs in PAD were identified.

Conclusions

Bleeding-related ADRs were highest in PV reports and the lowest in questionnaires, suggestive of under-reporting of ADRs considered as minor or less serious. High numbers of reported ADRs for rivaroxaban compared to dabigatran and apixaban possibly reflect consumption trends. Consumption trends show that rivaroxaban is the most used NOAC. Differences in reported ADRs could be due to differences in consumption trends, differences in safety profiles of medication or reporting bias. ADRs are more likely to be reported for novel medications such as NOACs which lack safety information compared to conventional drugs such as aspirin. Two studies show that when added to aspirin, NOACs may have favourable efficacy outcomes compared to aspirin alone. More data on the safety and efficacy of NOACs is necessary to help determine the risk-benefit ratio of therapy.

Keywords: aspirin, novel oral anticoagulants, comparative analysis, adverse drug reactions, peripheral artery disease