CHAPTER 1: INTRODUCTION

This chapter is a reflection of the general lay-out of the study and includes a problem statement, research objectives, and research methods, division of chapters, time schedule and references.

1.1 PROBLEM STATEMENT

Warfarin is an anticoagulant that is used for a wide range of prophylactic and therapeutic conditions all across the medical spectrum (Egred *et al.*, 2005:294). It has been used as an anti-coagulant since the 1950s (Katzung *et al.*, 2009:594). It has been estimated that in the United States alone 20 million prescriptions are written for warfarin each year. Katzung *et al.* (2009:594) classify warfarin as a direct thrombin inhibitor. It interferes with the conversion of the inactive form of prothrombin to the active form of prothrombin by the inhibition of the vitamin K cycle. Warfarin inhibits the formation of the reduced form of vitamin K (vitamin KH_2) from the oxidised form of vitamin K (vitamin KO) by inhibiting the enzyme Vitamin K epoxide reductase. Vitamin K acts as a co-enzyme for the γ-carboxylation of inactive prothrombin to active prothrombin (Hirsh *et al.*, 2003:1633).

Warfarin is indicated for a wide range of conditions. It is used in the prophylactic treatment and treatment of both venous and pulmonary thrombo-embolisms. It is also used in the prevention of stroke in patients with atrial fibrillation (Diener *et al.*, 2010:1157).

Warfarin therapy is influenced by many factors. This is why it can become very complicated for one individual patient. Warfarin in general is not a safe drug, although it is widely prescribed for a number of cardiac and blood-related conditions (Gibbon, 2008:612). The problem with warfarin is that it has a narrow therapeutic index and therefore it has many problems concerning over- or under-dosage (Jonas & McLeod, 2009:375). The most common side-effects experienced in treatment with warfarin are bleeding or haemorrhage. Other side-effects include skin necrosis and decreased bone strength (Simon *et al.*, 2002:353). Warfarin is also teratogenic. It causes nasal hypoplasia, stippled epiphyses and distal extremity hypoplasia in the fetus when taken during the first trimester of pregnancy (Simon *et al.*, 2002:353).

There is no standard dosing regimen for warfarin and dosing should be tailored for every individual. The standard initial dosage is 5 mg per day (Hirsh *et al.*, 2003:1633). The international normalised ratio (INR) is used to measure the effect warfarin has on

prothrombin. This is a value based on the prothrombin time (PT). The value is also based on each individual clinical laboratory's thromboplastin reagent lot. This lot is compared with an international standardised value that the World Health Organization has established (Leiker *et al.*, 2009:227). The PT and INR are used to determine how long it takes for blood to clot. In other words, the longer the PT the longer it takes for blood to clot (Mosby, 2009:1533). The optimum INR value depends on the condition that should be treated. For the prophylaxis or treatment of thrombo-embolism, the INR should be in the range of 2-3. For patients who received artificial heart valves or who are continuously at risk of thrombo-embolism, the INR should be in the range of 2.5-3.5 (Katzung *et al.*, 2009:596). In the initial stage of treatment the INR should be monitored on a regular basis until a stable dose-response relationship has been achieved. Thereafter the INR can be tested less often and a maintenance dose can be given (Hirsh *et al.*, 2003:1633).

Warfarin in the blood is more than 99% bound to the plasma protein, albumin. This means that only a small amount is unbound and free to be metabolised (Fitzpatrick *et al.*, 2004:11). The drug is absorbed in the gastro-intestinal tract, and maximum blood concentrations are reached 90 minutes after it has been orally administered (Hirsh *et al.*, 2003:1633).

Warfarin is a mixture of two isomers, the R-isomer and the S-isomer. These 2 isomers are both metabolised in the liver by the cytochrome P450 enzyme system (Hirsh *et al.*, 2003:1633). It is because of this that warfarin interacts with many other drugs that are also metabolised by this system in the liver. This causes changes in the blood concentration of warfarin that can lead to increased risk of bleeding or for embolism. Other factors such as the stereochemistry of a drug, plasma protein binding, and many others also influence the blood concentration of warfarin. Drug interactions can be divided into 2 major effects, namely pharmacokinetic effects and pharmacodynamic effects. These effects can increase or decrease the PT by an array of mechanisms. Some drugs that can increase the PT by several mechanisms are amiodarone, cimetidine, disulfiram, metronidazole, fluconazole, phenylbutazone, sulfinpyrazone, trimethoprim-sulfamethoxazole, aspirin, third generation cephalosporins and heparin. Some drugs that can decrease the PT are barbiturates, cholestyramine, rifampin, diuretics and vitamin K. Some of these mechanisms include the induction or inhibition of the cytochrome P450 system, reduced plasma protein binding, synergism, competitive antagonism, and many others (Katzung *et al.*, 2009:596). The above list of drugs that interact with warfarin includes only a handful of all the drugs that interact with it. The actual list is extensive and is still growing.

There are more factors that should be considered before starting warfarin therapy. Age, race, weight, diet, illness, smoking and adherence to the drug are all factors that may

influence the dose of warfarin. Studies show that the required maintenance dose for warfarin decreases as the patient gets older (Jonas & McLeod, 2009:375). This is due to a decrease in drug clearance and an increase in the responsiveness to the drug. The presence of genetic variants leads to different dosing requirements between different races. This leads to the fact that African-Americans need a higher dose of warfarin where Asians need a lower dose when compared to Caucasians (Jonas & McLeod, 2009:375). Alcohol consumption and vitamin K intake are dietary factors that can influence warfarin therapy (Jonas & McLeod, 2009:375). Liver disease, malnutrition, heart failure and other illnesses all have an effect on the doses (Jonas & McLeod, 2009:375). Genetic variations in the cytochrome P4502C9 enzymes may lead to differences in plasma protein binding and elimination half-life (Linder, 2001:9). This may also lead to hypersensitivity or resistance to warfarin, thus adjustments to doses (Linder, 2001:9).

It is clear that warfarin is a drug that should not be prescribed without thorough investigation of the patient's medical history. As has been stated before, bleeding is one of the major risks of warfarin therapy. It is also evident that the co-prescribing of other drugs with warfarin increases this risk for bleeding and thus may lead to serious consequences. It is a serious concern when warfarin is prescribed together with interacting drugs. According to a study done in Scotland, 68% of the study population had been prescribed warfarin together with at least one drug that could potentially interact with it (Snaith *et al.*, 2008:207). Some of these drugs that were co-prescribed were antibiotics, anti-inflammatory drugs (non-selective NSAIDs) and other antithrombic drugs such as fibrinolytics. Many of these patients received repeat prescriptions for these drugs while they were on warfarin therapy. This practice leads to frequent hospital visits regarding drug-drug interactions with warfarin (Snaith *et al.*, 2008:207). Similar results were found in a study done in Ireland where 31.6% of the study population, who had been using warfarin for longer than one month, received a prescription for at least one interacting drug in the time the study was done (Johnson & Dack, 1992:119). What is more, 5.7% of the study population had been prescribed more than one drug with a potential interaction with warfarin. The majority of the drugs prescribed were NSAIDs and aspirin (Johnson & Dack, 1992:119).

1.2 RESEARCH QUESTIONS

On the basis of the above-mentioned discussion, the following research questions can be formulated:

- Are there any differences in prescribing patterns for warfarin?
- What is the prevalence of drug-drug interactions on warfarin prescriptions?

- Is there a difference in the prevalence of drug-drug interactions of warfarin prescriptions?
- Are there any changes in the prescribed daily dosage (PDD) of warfarin when interacting drugs are prescribed?
- Do prescribers initially prescribe the minimum standard dose of 5 mg per day at the start of warfarin therapy?
- Does age influence the prescribing patterns of warfarin?
- Is there a difference in the prescribing patterns of warfarin between specialists and general practitioners?

1.3 RESEARCH OBJECTIVES

This research objectives include a general objective, as well as specific objectives.

1.3.1 General research objective

The general research objective of this study is to compare the prescribing patterns, as well as the prevalence of drug-drug interactions (PDDI) of warfarin prescriptions in a South African private health care setting for the period 2005 to 2010 by using a medicine claims database.

1.3.2 Specific research objectives

The research project consists of two phases, namely a literature review and an empirical investigation. The empirical investigation is discussed in section 3.2.2.1. The research objectives of phase one include the following:

1.3.2.1 Phase 1: Literature review

The specific research objectives of the literature review include the following:

- To describe the indication and management of warfarin therapy;
- To describe from the literature the process of monitoring patients on warfarin therapy;
- To investigate the pharmacokinetic and pharmacodynamic characteristics of warfarin that may lead to potential drug-drug interactions with warfarin; and
- To describe the factors that may influence the appropriate prescription of warfarin therapy.

1.3.2.2 Phase 2: Empirical Investigation

The specific research objectives of the empirical investigation include the following:

- To investigate the prescribing patterns of warfarin in a part of the private health care sector of South Africa;
- To investigate the prevalence of co-prescribing of potentially interacting drugs with warfarin in South Africa over a six year period, 2005-2010;
- To assess whether warfarin treatment is changed when prescribed together with potentially interacting drugs.

1.4 RESEARCH METHODOLOGY

The research consists of two phases, namely a literature review and an empirical investigation.

1.4.1 Phase 1: Literature review

This step of the research project will focus on a review of the most recent publications regarding the prevalence of patients on warfarin therapy, the reasons for drug-drug interactions with warfarin, and the factors that influence the prescribing patterns of warfarin.

1.4.1.1 Literature study

A literature study was done using a variety of resources that included journals, textbooks and other sources such as the Internet.

The literature study consists of a review that is divided into three major parts. The first part mainly consists of a background of warfarin itself. A short history is given on how warfarin came to be in clinical practice, thereafter the pharmacological classification and indication of warfarin follow. The pharmacokinetics and pharmacodynamics of warfarin is thoroughly discussed. These two sections comprise numerous subsections in which a thorough investigation is undertaken on the different aspects of warfarin and warfarin therapy. Under pharmacokinetics, including factors such as basic chemistry, absorption, distribution, metabolism, warfarin resistance and the elimination of warfarin are discussed. Under pharmacodynamics, factors such as the mechanism of action of warfarin, side-effects of warfarin and the dosage and monitoring of warfarin therapy were discussed. These are all important factors that have an influence on warfarin therapy. This part of the literature study

also includes the different definitions of drug-drug interactions, as well as a broad classification and discussion of the different drug-drug interactions.

The second part of the literature study focuses on clinical problem areas when it comes to drug-drug interactions. Definitions are given for terms such as adverse drug event and polypharmacy and the problems associated with them. A large portion of this part of the literature study is attributed to the significance ratings of drug interactions. The focus is primarily on drugs that have a potential interaction with warfarin and the significance of these interactions.

The final part of the literature study focuses on other anticoagulants and their place in anticoagulant therapy. A broad classification of all the anticoagulants is provided, as well as a discussion on the mechanism of action, clinical use and the most common side-effects associated with these anticoagulants. The focus is on the anticoagulants currently in use in South Africa.

1.4.2 Phase 2: Empirical investigation

The empirical investigation compromised several steps that will be discussed in Chapter 3.

1.4.2.1 Research design

This was a cross-sectional, observational or qualitative study and the empirical investigation was done retrospectively on warfarin products.

1.4.2.2 Data source and study population

A retrospective drug utilisation review will be done on data provided by the database of a pharmaceutical benefit management company (PBM). The study period will range from 1 January 2005 to 31 December 2010. The study population consisted of the total data collected from the medicine claims database for the six year study period. Warfarin prescriptions were extracted from the total database.

1.4.2.3 Research measurements

- Prevalence, "the number of all new and old cases of a disease or occurrences of an event during a particular period" (Mosby, 2009:1512) (refer to section 3.3.5.1);
- Prescribed daily dosage (PDD), "the average dose prescribed according to a representative sample of prescriptions" (Cosentino *et al.,* 2000:513) (refer to section 3.3.5.2);

- Significance ratings: drug interactions are assigned a significance rating ascending order of 1 to 5 according to the severity and documentation level of the DDI (Tatro, 2011: xv) (refer to section 3.3.5.3).

1.4.2.4 Data analysis

Data were collected on the overall prescribing patterns of medicine items. Data on warfarin products were extracted to analyse the different prescribing patterns of warfarin products. Then the co-prescribing of drugs with a potential DDI with warfarin was analysed. The data analysis was done by means of the Statistical Analysis System, SAS (SAS Institute Inc., 2006).

1.4.2.5 Ethical considerations

Medicine claims data were provided by a South African pharmaceutical benefit management company. Confidentiality of the patients, pharmacies, medical practices and medical schemes was ensured by a numbering system. Within the medicine claims databases the individual patients and prescribers could not be identified and the study was concluded anonymously. Ethical approval was obtained at the North-West University (NWU-0046-08S5).

1.5 DIVISION OF CHAPTERS

The chapters are divided as follows:

- Chapter 1: Introduction
- Chapter 2: Warfarin treatment and the patient
- Chapter 3: Empirical Investigation
- Chapter 4: Results and Discussion
- Chapter 5: Conclusion and Recommendations

1.6 CHAPTER SUMMARY

A broad outline of what can be expected from this dissertation was given in this chapter. Firstly, the problem statement is given. This includes a discussion of why warfarin therapy is important but at the same time very problematic. The research questions followed which involve carefully selected questions that when answered, will cover all the basic objectives of

this study. The research objectives included the general and specific research objectives. Phase 1 of the specific objectives was also shortly discussed. The research methodology included among others, a discussion of what can be expected of the literature study in Chapter 2. The penultimate section included the type of research and topics such as the fields of study and the classification systems used in the study. Finally, the division of chapters of this dissertation was outlined.