Chapter Two

Literature Review

2.1 Introduction

Chapter One provided an introduction and background to the study by presenting the main purpose of the study, identifying and summarising the gaps in prior research conducted in this field and identifying the research problem. This was followed by a description of the research design and the methodology employed in the study, and these in turn by definitions and the key assumptions of the study. Lastly, an outline of the thesis was presented.

This chapter provides a critical analysis of the relevant literature pertaining to the research problem. The research question was introduced in Chapter One, and is here restated for convenience, with the aims and objectives of the study integrated throughout the chapter: Are episodes of over-anticoagulation potentially preventable or unforeseeable?

The complexities of warfarin are such that it would be impossible and also unnecessary in this thesis to discuss in detail its complex mode of actions. What is intended, however, is to provide a brief but crucially important account of its mechanisms of anticoagulant and antithrombotic activity and pharmacokinetics in the body in order to appreciate the difficulties encountered by clinicians in obtaining and maintaining optimal anticoagulant control. Additionally, it is important to discuss the bleeding complications associated with warfarin therapy and the variables thought to increase the anticoagulant effect of warfarin, that is, drug and food interactions, the effect of age, and patient education and degree of compliance while receiving warfarin therapy. Additionally, this chapter provides a comprehensive review of the current literature concerned with the association between the frequency of monitoring and INR control and the effectiveness of anticoagulation among patients discharged from hospital.

The chapter concludes with an extensive review and analysis of the current literature on trends in the management and control of warfarin therapy in both the hospital setting and the community. In doing so, the unresolved problems that persist today in maintaining the optimal control and management of warfarin therapy and the possible directions of care for the future, are discussed.

2.2 Identification of literature and modes of access

The review of the literature included national and international information gathered from electronic computerised databases, textbooks, consultation with experts in the field, medical and nursing journals and published pamphlets.

The researcher accessed the relevant computerised literature databases and entered combinations of subject keywords and names of key authors in the field into the databases. The databases searched included the following:

- MEDical Literature Analysis and Retrieval System Online (MEDLINE) (the publicly available version, known as Pubmed)
- Cumulative Index of Nursing and Allied Health Literature (CINAHL)
- Medscape Professional/Medscape Health
- Expanded Academic ASAP
- Proquest and SALUS (South Australian Health Services Libraries Consortium)

Information was also accessed via electronic search engines on the Internet from the 'Cochrane' sites, the Web Resource Centre via Bill Trochim's Centre for Social Research Methods (Yahoo & Google) and metacrawler.com, which searches all of the leading engines at once (Yahoo, Google and Ask Jeeves).

2.3 An introduction to warfarin therapy

Although the clinical effectiveness of warfarin as an anticoagulant in the prevention and treatment of thromboembolic disease has long been established (Panneerselvam et al. 1998), it is a potentially hazardous drug and can cause life-threatening haemorrhagic complications (Campbell et al. 2001). Warfarin causes overall bleeding complications in 3-10% of patients on warfarin per year (Campbell et al. 2001), major bleeding complications leading to death or hospitalisation in 1.2-8.1% of people during each year of long-term warfarin therapy and intracranial bleeding in approximately 0.1-0.5% of people during each year of therapy (Gallus et al. 2000). However, it is likely that warfarin will remain the only widely available oral anticoagulant agent in the foreseeable future (Garcia et al. 2005).

Because of warfarin's proven effectiveness. the number of patients receiving warfarin therapy has dramatically increased worldwide and in Australia (Sudlow et al. 1995). In the United Kingdom (UK) an estimated 10% year-on-year increase is expected for the next decade with approximately 500,000 patients currently taking warfarin (Murray 2003). According to a recent review by Glasheen (2005), annual retail sales exceed $400 million in the US. And according to Campbell et al. (2001:86), 'warfarin is the most widely used oral anticoagulant in Australia'. Borosak, Choo and Street (2004) reported that in 2001 in Australia almost 1.9 million out-of-hospital prescriptions were dispensed for warfarin at a cost of $8.3 million to the Pharmaceutical Benefits Scheme (PBS) and Repatriation Pharmaceutical Benefits Scheme (RPBS).

Although reports from the Australian Pharmaceutical Index (2004) indicate that warfarin use in Australia has increased between 6-9% per annum in the last four years and that current growth stands at approximately 9% per year, with approximately 200,000 patients currently taking warfarin in Australia (Bereznicki et al. 2006), according to several studies it is still an underused drug, particularly in the high-risk older population. The reason is thought to be partly the unpredictability of the drug and a fear of bleeding complications (Dudley 2000; Go et al. 1999; Kagansky et al. 2004; Sudlow et al. 1998).

Despite the proven effectiveness and the increasing worldwide use of warfarin, the maintenance and control of the INR within the optimal target range remains a difficult and complex task (Vadher, Patterson & Leaning 1997). Furthermore, questions remain as to the risks and the management of episodes of over-anticoagulation (Baker et al. 2004). The desirable range of the INR is usually 2.0-3.0 for a patient to be effectively anticoagulated, although a slightly higher level may be indicated in a few clinical conditions (Gallus et al. 2000).

Several studies have shown that excessive anticoagulation with a prolonged INR above 4.0 increases the risk of bleeding complications exponentially (Gallus et al. 2000; Levine et al. 2001; Panneerselvam et al. 1998). Additionally, according to several studies, approximately one in six INR values will exceed the desired range, with the resultant risk of a major bleed being approximately 5% in the two weeks following an INR result greater than 6.0 if the patient is treated with warfarin withdrawal alone (Hylek et al. 2000; Kearon et al. 1999; Oden & Fahlen 2002). Research also indicates that patients are at the greatest risk of bleeding in the first few months of treatment (Campbell et al. 2001; Linkins, Choi & Douketis 2003; Vadher, Patterson & Leaning 1997).

According to Vadher, Patterson and Leaning (1997), poor control of the INR may be due to a number of factors, including the complex pharmacology of warfarin, failure of doctors and nurses to follow guidelines and the inexperience of trainee doctors to make appropriate dosing and follow-up decisions. Additional factors may include the setting of an inappropriate INR target, patient-specific factors such as older age, the presence of co-morbid conditions and the use of concomitant drugs (Levine et al. 2001). Additionally, Campbell et al. (2001) postulated that patients who have a poor understanding of warfarin and its potential adverse effects are more likely to be non-compliant than those who receive sufficient education regarding warfarin therapy.

In 1992 'adverse events arising from warfarin use in Australia were estimated in this study to cost over $100 million per annum in direct hospital costs alone' (Rigby, Clark & Runciman 1999:10). Thus, for the benefits of warfarin therapy to be extended to a wider range of patients, particularly to older patients who may be prone to an increased number of co-morbidities and who therefore may be at a higher risk of bleeding complications, more attention to anticoagulant control is required. According to Baker et al. (2004), through an understanding of the pharmacokinetics and pharmacodynamics of warfarin and the use of preventative strategies published as consensus guidelines, bleeding risks can be minimised. Thus, frequency of monitoring, the number of major bleeding events, the degree of compliance and level of education of patients taking warfarin and the current medical trends in the management of warfarin therapy will be further investigated in this study. Furthermore, the question whether episodes of over-anticoagulation are potentially preventable or unforeseeable will be investigated.

2.3.1 Pharmacology of warfarin

Despite the fact that warfarin was first synthesised more than fifty years ago and has been in clinical use for more than forty years, comprehensive knowledge of its metabolic characteristics have only recently been elucidated and probably remain incomplete today (Kaminsky & Zhang 1997). Confusion remains regarding dosage, frequency of monitoring, management of over-anticoagulation, to whom it should be administered and whether the risk:benefit ratio justifies its administration in certain clinical conditions (Baker et al. 2004; Hirsh et al. 1995; Wessler & Gitel 1984). According to Wessler and Gitel (1984) and Hirsh et al. (2003), some of the uncertainty in these areas of confusion

persists because of an incomplete understanding, even today, of the molecular biology and pathologic physiology of the thrombotic process and the ways in which warfarin affects those phenomena. Additionally, scepticism about the relevance of data obtained in studies in animals to the thrombotic process in humans and the inaccuracies and shortfalling of researchers in determining the limitations encountered in clinical trials contribute to uncertainties persisting (Wessler & Gitel 1984).

Although warfarin can be administered in an injectable form, it is almost always given in oral form (Hirsh et al. 1998). Warfarin is a coumarin derivative and produces its anticoagulant effect by interfering with the cyclic inter-conversion of vitamin K and by inhibiting carboxylation of the regulatory anticoagulant proteins C and S. Vitamin K is required for the carboxylation of glutamate residues to γ-carboxyglutamates of vitamin K-dependent proteins for biological action. These proteins include the coagulant factors II, VII, IX and X. Carboxylation promotes the binding of these coagulant factors to phospholipid surfaces, thereby accelerating blood coagulation. The process of γ-carboxylation requires the reduced form of vitamin K, vitamin KH_2 for biological activity. Warfarin blocks the formation of vitamin KH_2 by inhibiting the enzyme vitamin K epoxide reductase (Hirsh et al. 2003). As a result of inhibiting this cycle, partially decarboxylated proteins with reduced coagulant activity are produced by the liver (Malhotra, Nesheim & Mann 1985).

The degree of reduced coagulant activity is dependent on the dose administered (Ho & Brighton 2002). Warfarin has a narrow therapeutic index, hence the need to individualise the dosage (Ho & Brighton 2002). The production of functional vitamin K dependent clotting factors is reduced by approximately 30-50% when therapeutic doses of warfarin are administered (Majerus et al. n.d. cited in Goodman Gilman et al. 1991:1318).

Although warfarin acts quickly to inhibit clotting factor synthesis, it has no direct effect on an already established thrombus. As a result, coagulation remains unaffected until those clotting factors that were present prior to the administration of warfarin decay. Because the decay of clotting factors has a half-life of between 6 hours to 2.5 days, depending on the clotting factor under consideration, the initial responses to warfarin may not be evident for 8-12 hours after the drug has been administered. Thus peak effects may not be seen for several days. Consequently, following discontinuation, coagulation remains inhibited for 2-5 days due to the long half-life of warfarin itself (Lehne et al. 1990).

The goal of treatment is to administer the lowest dose of anticoagulant in order to prevent further extension of the formed clot and secondary thromboembolic complications, which may result in serious or fatal sequelae (Mosby 1997).

Low doses of vitamin K_1 (phytonadione) will overcome the effect of warfarin because vitamin K_1 bypasses vitamin K epoxide reductase, but doses greater than 5 mg may cause the patient to become resistant for up to a week (Hirsh et al. 2003).

2.3.2 Pharmacokinetics and pharmacodynamics of warfarin

Warfarin is a racemic mixture of the active isomers, the R and S forms in approximately equal proportions (Hirsh et al. 2003); however, the S form of isomer reportedly exhibits 2-5 times more anticoagulant activity than the R form in humans and has a more rapid clearance rate (Mosby 1997). A study by Kaminsky and Zhang (1997) showed that S-warfarin is metabolised mainly to its major metabolite, S-7-hydroxy-warfarin, and to a much lesser extent, to S-6-hydroxy-warfarin, almost exclusively by the cytochrome P450 system and in particular, the CYP2C9 isoenzyme. The drug is rapidly and essentially completely absorbed from the gastrointestinal tract, reportedly reaching maximum blood concentrations in healthy persons 90 minutes after ingestion (Breckenridge 1978), although a report by Shetty, Fennerty and Routledge (1989) observed peak plasma concentrations between 0.3-4 hours. The overall bioavailability is not changed by the presence of food in the gut, but the rate of absorption may be affected and hence the drug should be taken on an empty stomach (Palareti & Legnani 1996). The half-life of R-warfarin sodium has been reported to range from 37-89 hours while the half-life of S-warfarin sodium ranges from 21-43 hours (Mosby 1997). Thus the effective mean half-life is approximately 40 hours (Boots Healthcare Australia 2000 cited in Baker et al. 2004: 493) Because of these considerable variations in the dose-response relationship, the dosage requires close monitoring to prevent overdosage or underdosage (Hirsh et al. 1995).

Because warfarin is highly bound to mainly albumin (99%), a plasma protein, it cannot exit the bloodstream and become distributed to spaces outside the vasculature, hence the volume of distribution is comparably small at 0.14 litre/kg (Majerus et al. n.d. cited in Goodman Gilman et al. 1991:1319). However, those warfarin molecules that remain free, approximately 1%, can readily cross membranes, including those of the placenta and

mammary glands and it is this small fraction of the drug that is responsible for the anticoagulant effect (Palareti & Legnani 1996). Thus, displacement from protein binding sites caused by other drugs may cause an increase in the intensity of the effect of warfarin and a resultant risk of haemorrhage (Lehne et al. 1990). Within 24 hours of administration, an anticoagulant effect is noted but a peak effect may not be noted until approximately 72-96 hours after administration. The duration of action of a single dose may be 2-5 days, thus the impact may become more pronounced as effects of daily maintenance doses overlap (Mosby 1997).

The potential for interactions to occur with warfarin therapy resulting in changes in the anticoagulant response is widely recognised among health professionals. The list of factors considered to exert an effect on the anticoagulant response of warfarin is large and forever expanding (Majerus et al. n.d. cited in Goodman Gilman et al. 1991:1319). The anticoagulant response to warfarin is influenced by both pharmacokinetic factors which affect its absorption or metabolic clearance and pharmacodynamic factors which affect its haemostatic response to given concentrations of the drug (Hirsh et al. 2003). Variability may result from inaccuracies in laboratory testing, patient non-compliance or miscommunication between patient and doctor (Hirsh et al. 2003). Additionally, such factors as travel and changes in diet and environmental and physical factors, alone or in combination, may influence the response of patients to warfarin (Mosby 1997).

Furthermore, according to Breckenridge (1978), the relationship between the dose of warfarin and the response may be influenced by genetic factors. Some of the genetic factors include common mutations in the gene coding for cytochrome P450 and the hepatic enzyme responsible for oxidation metabolism of the warfarin S isomer. Warfarin is normally metabolised by a variety of cytochrome P450, hepatic microsomal enzymes, to inactive hydroxylated metabolites and by reductases to reduced metabolites (Hirsh et al. 1998). Hence, the elimination of warfarin from the body is almost entirely by metabolism whereby the inactive metabolites are excreted in the urine and stools (Majerus et al. n.d. cited in Goodman Gilman et al. 1991:1319).

2.3.3 Clinical indications for warfarin therapy

Information derived from well-designed clinical trials, in a variety of disease conditions, has established the clinical effectiveness of warfarin in the treatment

> for primary and secondary prevention of venous thromboembolism, for prevention of systemic embolism in patients with prosthetic heart valves or AF, for prevention of acute myocardial infarction (AMI) in patients with peripheral arterial disease and in men otherwise at high risk, and for prevention of stroke, recurrent infarction, or death in patients with AMI. (The Medical Research Council's General Practice Research Framework 1998 quoted in Hirsh et al. 2003: 1642)

Additionally, oral anticoagulants are 'indicated for prevention of systemic embolism in high-risk patients with mitral stenosis and in patients with presumed systemic embolism, either cryptogenic or in association with a patent foramen ovale', even though the effectiveness of warfarin in these conditions has not yet been proven by randomised trials (Hirsh et al. 2003:1642).

2.3.4 Anticoagulant effect of warfarin

As previously mentioned, the anticoagulant effect of warfarin is dependent on the decay and clearance of functional clotting factors already present from the systemic circulation after administration of the drug initially and is reflected in changes in the INR (Glasheen 2005). The decay of those clotting factors is determined by their half-lives, which vary from 6 hours to 2.5 days (Lehne et al. 1990). The earliest change in the INR is typically noted 24-36 hours after a dose of warfarin is administered, but these early changes are deceptive because they do not reflect the body's physiological ability to halt clot expansion or form new thromboses. They occur due to the clearance of functional factor VII, which has a half-life of 6 hours, and functional factor IX, which has a half-life of 24 hours (Hirsh et al. 1995). Thus the initial increase seen in the INR is not thought to be associated with a clinically significant antithrombotic effect because of the presence of prothrombin (Baker et al. 2004).

2.3.5 Antithrombotic effect of warfarin

The antithrombotic effect of warfarin is usually not present until approximately the fifth day after initiation of warfarin therapy and is defined as the body's inability to expand or form clots. This effect is dependent on the clearance of functional factor II (prothrombin) which has a half-life of approximately 60-72 hours, thus preventing a true antithrombotic effect from being achieved for up to 96 hours (Hirsh et al. 1995).

While it is generally thought that all four vitamin K-dependent coagulation factors are required to be inhibited to achieve an antithrombotic effect, there is some indirect evidence from studies by Wessler and Gitel (1984), Zivelin, Roa and Rapaport (1993) and Patel et al. (1996) to support the hypothesis that the reduction of factor II (prothrombin) and possibly factor X is more important than the reduction of factors VII and IX.

It is the conventional view that the antithrombotic effect of warfarin reflects its anticoagulant effect. According to Hirsh et al. (2003), the two are quite separate and the difference between the anticoagulant effect and the antithrombotic effect of warfarin is an important aspect that needs to be understood and acted upon in clinical practice. Observations by Weitz et al. (1990) noted that clot-bound thrombin was an important mediator of clot growth. Subsequently, Patel et al. (1996) noted that a reduction of prothrombin levels decreased the amount of thrombin that can be generated and bound to fibrin and thus reduced the thrombogenicity of the clot. Because thrombin bound to fibrin is enzymatically active and protected from inactivation, it acts as a reservoir that can amplify its own generation by activating platelets and factors V and VIII. Thus, Hirsh et al. (2003) postulated that the concept of the antithrombotic effect of warfarin actually reflects its ability to reduce the prothrombin levels, which is important for the following two reasons.

First, the basis for commencing patients on heparin for the initial four or five days overlapping with warfarin therapy until the prothrombin time (INR) is prolonged into the therapeutic range is affirmed (Hirsh et al. 2003), and second, it supports the rationale for avoiding a loading dose of warfarin on initiation of therapy in exchange for administering a maintenance dose of approximately 5 mg daily (Harrison et al. 1997). The authors of this study found that, when evaluating the basis for a loading dose of warfarin on initiation of therapy, the rate of lowering prothrombin levels was similar when either a 5-mg or a 10-mg initial dose of warfarin was given. Additionally, they found that when a loading dose of 10 mg was given, anticoagulant protein C activity was reduced significantly more rapidly and more patients were excessively anticoagulated with a prolonged INR>3.0. The effect of significantly reduced protein C levels, and near-normal levels of factors II and X, during the first 36 hours of warfarin therapy could possibly produce a paradoxical consequence of a hypercoagulable state. Thus, loading doses may potentially create clot formation and/or expansion by limiting the production of proteins C and S, which have significantly shorter half-lives than prothrombin. While Harrison et

al. (1997) recognised limitations to their study, the findings suggested that both 5-mg and 10-mg regimes for dosing resulted in therapeutic INRs in most patients by the fifth day of treatment. Consequently, Hirsh et al. (2003) recommend that the concurrent use of heparin in the first 4-5 days is imperative and the practice of using a loading dose should be abandoned because it has no effect on the inhibition of thrombosis.

2.4 Bleeding complications associated with warfarin therapy

The preceding sections have introduced warfarin, considered the pharmacokinetics and dynamics of warfarin and discussed the difference between the anticoagulant and antithrombotic effects of warfarin.

The most common complication associated with warfarin therapy is bleeding (Baker et al. 2004; Levine, Raskob & Hirsh 1989). For the purpose of this study, this review will only discuss those variables that are generally considered to increase the risk of bleeding complications. Those variables and conditions under which the patient may suffer inadequate levels of anticoagulation will not be addressed.

The critical issue in the administration of warfarin therapy to prevent or treat thromboembolism is whether the benefit of therapy outweighs the risk of bleeding in an individual (Landefeld & Goldman 1989). Since the clinical utilisation of warfarin as an anticoagulant for the treatment and prevention of thromboembolic diseases more than forty years ago, there have been many references to studies which addressed the issues surrounding the risk of bleeding complications. While it is neither feasible nor pertinent to follow up all of those references here, it is the intention of the researcher to discuss the most significant and robust of those studies which have contributed to the bulk of knowledge as we know it today.

Few studies published before the 1990s have produced reliable data to estimate the true frequency of bleeding complications because of methodological limitations (van der Meer et al. 1993). There is a paucity of early studies that report on the safety of warfarin, on the success in maintaining patients within the nominated therapeutic range or on the total time the patients in the study were on warfarin therapy. Thus, these studies were more interested in reporting the efficacy of the treatment. Additionally, documentation of clinical risk factors was lacking in many reports as was information on the number of patients at risk at the time of a bleed, making it difficult to determine accurate bleeding

rates (Levine, Raskob & Hirsh 1989). Furthermore, according to Hirsh (1987), patients in many of the early studies received excessive doses of warfarin, rendering the studies irrelevant in respect of estimating true bleeding risks. Further discrepancies, such as small sample sizes, unique attributes of a single institution's referral base and practice patterns and stringent eligibility criteria may have also limited the value of many early studies (Fihn et al. 1993). Moreover, prior to the development of the INR for monitoring warfarin in the 1980s, Prothrombin Time, expressed as PT ratio, was used and considered to be very imprecise because of the marked variability in the responsiveness of the thrombo-plastins commonly used (Hirsh et al. 2003). These differences in thromboplastin responsiveness in oral anticoagulant dosing was responsible for excessive and erratic anticoagulation in North America during this time, and it was the recognition of these shortcomings that stimulated the development of the INR standard for monitoring oral anticoagulant therapy (Hirsh et al. 2003). Thus, many results of studies carried out during this period may not truly reflect accurate data. Because of the many limitations of these studies, this chapter will mention some of them only briefly and instead examine closely the more recent and methodologically sound and robust studies.

Many of the reports addressing the risk of bleeding complications associated with warfarin therapy appeared during the 1960s and the 1970s. Several studies reported that the presence of an underlying tumour or lesion might be the cause of a bleed (Davis et al. 1977; Michaels 1962; Mosley et al. 1963; Zweifler 1962). Most commonly involved sites identified for these bleeds were the gastro-intestinal and genito-urinary tracts and it was recommended that an underlying lesion should be considered in the differential diagnosis of anticoagulated patients who developed a bleed (Zweifler 1962).

One of the first noteworthy studies that identified risk factors that contributed to present-day knowledge was a patient record review conducted by Landefeld and Goldman (1989). The study, which included 565 subjects starting outpatient warfarin therapy upon discharge from a university hospital in Cleveland, US, identified several independent risk factors for a major bleed. The risk factors identified included advanced patient age >65 years, the intensity of anticoagulant therapy, a history of stroke or gastrointestinal bleeding, the presence of a serious co-morbid condition or the presence of atrial fibrillation. Each 1.0 increment in prothrombin time-to-control ratio was associated with an 80% increase in odds ratio for a major bleed when a cohort sub-analysis was conducted. This was an important study because it was one of the first robust studies to

identify risk factors. Furthermore, the risk factors identified in this study have been identified as major risk factors for a bleed and ratified today by several authors (Campbell et al. 2001; Hirsh et al. 2003).

Importantly, Landefeld and Goldman (1989) observed a marked decrease in the monthly rate of major bleeds over the first year of outpatient therapy. According to the authors, a contributing factor to the increased rate of bleeding early in the course of therapy may have been a clinical occult, biologic predisposition to bleeding. Another contributing factor may have been that patients are often less well controlled at the start of therapy due to changes in warfarin doses, the discontinuity of care and factors that affect warfarin metabolism (Landefeld & Goldman 1989). These authors postulated that studies that examine non-inception cohorts and/or include patients who have resumed anticoagulant therapy are very likely to underestimate the true risk of bleeding by either missing early treatment events or excluding from any second course patients who had bled in the first course. Although the presence of an increased bleeding risk rate during the initial months of treatment was not found in several earlier studies (Forfar 1979; Gurwitz et al. 1988; Levine, Raskob & Hirsh 1986), many later studies (Fihn et al. 1993; Linkins, Choi & Douketis 2003; Palareti et al. 1996) have observed similar results as those discussed by Landefeld and Goldman (1989).

Following on from Landefeld and Goldman (1989), Fihn et al. (1993), in a retrospective cohort study involving 928 consecutive patients receiving 1103 courses of warfarin from five anticoagulation clinics in the US, attempted to further define risk factors for complications that occur during warfarin therapy. The authors determined that there were four independent risk factors for the first episode of a bleed. These factors included a mean prothrombin time ratio (PTR) of 2.0 (a PTR of 2.0 is the estimated equivalent of an INR of 4.6-5.3 in this study) or greater, a shorter duration of anticoagulation, a greater variability in the PTR and the presence of three or more co-morbid conditions. While age was not found to be a significant risk factor, women were found to have a relative risk for a first time serious bleed of 1.9 (CI, 1.3-3.0) after adjustment for intensity of treatment was made. Interestingly, the study did not find that race, an indication for anticoagulation, history of stroke or atrial fibrillation, hypertension, any intercurrent illness or use of potentially interfering medications had a significant effect on bleeding complications.

As in the study by Landefeld and Goldman (1989), a major factor for the risk of an initial bleed was found to be associated with how recently the warfarin therapy had been

commenced. PTR values in the study by Fihn et al. (1993) were often found to be erratic due to dosage adjustments made at the start of therapy. The risk was found to be greatest during the first three months of initiating therapy, which diminished gradually over the subsequent 2-3 years. Serious and life-threatening bleeding rates of 21 and 1.8 episodes per 100 patient-years, respectively, occurred during the first three months of therapy. Explanation for the increased risk was attributed to the same reasons as those found in the study by Landefeld and Goldman (1989).

Furthermore, when the PTR was 2.0 or greater, the incidence of a serious bleed was 26 events per 100 patient-years compared to 11 events per 100 patient-years when the PTR was in the range of 1.3-1.5 (relative risk, 3.0. 95% CI, 1.9-4.7; P<0.001). The cumulative incidence of a serious bleed when the PTR was 1.3-1.5 (estimated INR of 2.0-3.0, using typical North American PT reagents) was the same as when the PTR was 1.5-2.0 (estimated INR of 3.0-4.5). It was not until the PTR was <1.3 that the incidence per 100 patient-years dropped to 8.7. Because a PTR was used but not always noted in the medical records, and so an approximation of the desired target for each patient was computed, the data may not have truly reflected the frequency of bleeding complications and must be viewed as a serious methodological limitation. While the fatal and serious bleeding rates were substantially lower than those seen in previous studies (Gurwitz et al. 1988; Landefeld & Goldman 1989), Fihn et al. (1993) surmised that this might be attributed to two factors. First, all patients in the present study were followed by experienced practitioners in clinics dedicated to anticoagulation so the patients were more closely followed, and second, most of the patients were treated after 1986 and therefore received lower-intensity regimens of warfarin. However, the frequency of PTR monitoring was not documented, rendering it unfeasible to determine if infrequent PTR monitoring contributed to the erratic and increased PTR values during this early period after warfarin initiation.

Variations and instability in the PTR were also considered to be a significant risk factor for a bleed and were attributed to variations in drug metabolism, medication compliance, diet and use of other drugs or fluctuations in a co-existing illness, such as heart failure. It was found that patients who had more than four dosage adjustments per year experienced a bleed 25% more often than patients who had fewer adjustments (P=0.004) (Fihn et al. 1993).

A significant limitation acknowledged in the study by Fihn et al. (1993) was identified as a poorly defined definition of a major or minor bleed. Thus what may have been classified as a major bleed in this study may not have been classified as a major bleed in another study, causing significant discrepancies in the results. Several other limitations of missing data, inaccurate medical records and discrepancies in the reporting of INR and PTR values may have also impacted on the results of this study. This study did not report INR values, but instead calculated them retrospectively and in doing so, may have incurred significant variations from the original true readings. According to Bussey et al. (1992), variations in retrospectively calculated INRs may be incurred depending on the type of International Sensitivity Index (ISI) of the thromboplastin used. It is important to note, however, that although the authors acknowledged the above limitations to their study, they postulated that it should be possible to reduce the risk of bleeding complications during warfarin therapy by attending to modifiable and non-modifiable risk factors (Fihn et al. 1993). Furthermore, a key aspect of this study to note is the consistency in the findings of increased risk of bleeding associated with the initial months of treatment and instability in the PTR.

Landefeld and Beyth (1993), in an overall review and summary of published literature of the frequency, characteristics, predictors and prevention of anticoagulated-related bleeding up until this date, made the following findings. They reported that an average risk for major bleeding was approximately 3% per year and most often occurred in the gastro-intestinal tract, soft tissues and the urinary tract. Diagnostic evaluation of these bleeds led to identification of previously unknown lesions in approximately one third of cases. They reported that while intracranial bleeding was rare, it was often fatal when it occurred. The length of therapy was identified as a critical determinant of the overall risk of bleeding as was the intensity of the anticoagulant effect achieved. That is, the risk for a bleed was identified as approximately ten-fold higher during the initial month of therapy than it was after the first year and if the PTR value was greater than 2.0. The most important patient risk factors included a serious co-morbid illness, such as heart, kidney, liver and cerebrovascular disease and probably age (Landefeld & Beyth 1993). While it must be noted that these studies reviewed by Landefeld and Beyth (1993) had suffered many methodological limitations, as mentioned above, it is important to note that many of the findings identifying significant risk factors for bleeding complications have again

been established in later and more methodologically sound studies (Koo et al. 2004; Linkins, Choi & Douketis 2003; Levine et al. 2001).

Of the bleeding complications associated with warfarin therapy, intracranial haemorrhage is the most feared because of the frequently catastrophic outcomes resulting in death or severe neurologic disability (Hylek & Singer 1994). While previous prospective analytic studies by Fihn et al. (1993) and Landefeld and Goldman (1989) focused on major bleeding complications of warfarin therapy, they had included only a few cases of intracranial haemorrhage and as a result, independent risk factors for this complication had not been identified (Hylek & Singer 1994). In a case-control study conducted by Hylek and Singer (1994) in a Massachusetts general hospital from 1981-1991 that focused on intracranial haemorrhage exclusively, and included 121 eligible adults taking warfarin, the authors found that the dominant risk factor for both intracerebral and subdural haemorrhage was the level of the PTR value. Hylek and Singer (1994) found that the risk for both dramatically increased when a PTR value was above 2.0 (calculated INR value of 4.5 if using the typical North American PT reagent used at that time). According to these authors, the risk for intracerebral bleeding doubled for each 0.5 increase in the PTR value. Hylek and Singer (1994) postulated that the intensity of the anticoagulant therapy might pose an even greater risk for intracranial haemorrhage than first thought because, according to Hirsh (1992), the PTR was not standardised at that time and so variations in the PTR values were common. Additionally, the authors anticipated that even at the low end of the 'therapeutic' range of anticoagulant therapy (INR of 2.0-3.0), there might exist a monotonic risk because most of the intracranial haemorrhages that occurred in their study did so when the PTR was below 2.0. The PTR of 2.0 was calculated to correspond to an INR of 3.7-4.3 (Hylek & Singer 1994).

Age was considered to be another significant independent risk factor for both intracerebral and subdural haemorrhage, although it was more of a risk for subdural haemorrhage, nearly doubling the risk with each ten-year increase in age. Additional risk factors for intracerebral haemorrhage included a history of cerebrovascular disease and the presence of a prosthetic heart valve, while risk factors for a subdural haemorrhage included a history of AF, myocardial infarct and duration of warfarin therapy of more than five years (Hylek & Singer 1994). Interestingly, although the sample size was small, Landefeld and Goldman (1989) in their earlier study had reported a univariate relative risk of 6.6 for intracranial haemorrhage in patients who had a history of past or current

stroke. Most importantly, Hylek and Singer (1994) postulated that the intensity of anticoagulation might be more important in increasing the risk of intracranial haemorrhage among patients taking warfarin therapy rather than age itself. They found a dramatic increase in the risk for intracranial haemorrhage when the PTR value was greater than 2.0, and emphasised the importance of careful control of anticoagulation at the lowest effective intensity of treatment in all patients, but particularly in older patients (Hylek & Singer 1994).

In summary, it would appear that the occurrence of warfarin-associated intracerebral bleeds are associated with advancing age, the presence of cerebrovascular disease and the intensity of anticoagulation (Hart 2000; Hylek & Singer 1994; Rosand et al. 2004). According to Hart (2000), the presence and severity of hypertension is also an independent contributor to an increased risk of intracerebral bleeds with warfarin therapy. Additionally, Hart (2000) postulated that the initiation of warfarin therapy might expose an underlying predisposition to an intracerebral bleed, especially if the INR threshold is prolonged. But the author also stressed that this factor alone was not the single cause of an intracerebral bleed and that the patient's age among other features contributed to an increased risk (Hart 2000). There is no clear or practical method to accurately predict whether or not an individual patient will incur an intracerebral bleed at present, but Hart (2000) postulated that those patients over 75 years or who have a history of cerebrovascular disease would be more likely to incur a rate of intracerebral haemorrhage while receiving warfarin therapy of approximately 1% per year, even if the INR were maintained between 2-3. While Rosand et al. (2004) agreed with this supposition, data from their study indicated that this risk rose further as the INR increased and concluded that careful monitoring of the INR may reduce both the risk of developing an intracerebral bleed and the mortality rate of those bleeds that occur.

A large prospective study by Palareti et al. (1996), involving 34 Italian anticoagulation clinics and 2,745 consecutive patients from the beginning of their warfarin therapy, observed a 7.6% overall bleeding rate and a 1.1% major bleeding rate among the participants. The findings of this study were consistent with the results of the earlier study by Fihn et al. (1993), in that the authors found that the risk for a major bleed was higher during the initial 90 days of treatment, compared with later in the treatment (11.0 versus 6.3, $P<0.001$). Additionally, they found a fifth of the bleeding events occurred when the INR<2.0 (7.7 per 100 patient-years of follow-up), supporting the report by Landefeld and

Goldman (1989) that many bleeds may not be related to the intensity of anticoagulation, but to a local bleeding source that is unmasked by the anticoagulant therapy. The authors of this study also found, as did Fihn et al. (1993), that only a slight but significant increased risk in bleeding occurred when the INR was recorded between 3.0-4.4 but when the INR was recorded over 4.5, the risk became much greater (Palareti et al. 1996).

The rate of bleeding events was also found to be higher when the indication for warfarin treatment was peripheral and/or cerebrovascular disease as opposed to venous or other thromboembolic disease (12.5 versus 6.0 per 100 patient-years, $P<0.01$) and in patients 70 years or older (Palareti et al. 1996). These authors found that the annual risk for a major bleed in patients over the age of 70 years was 2.9% with no major bleeds occurring in patients less than 50 years. An important aspect of this study was the use of the INR, which increased the reliability of measuring the level of anticoagulation and allowed for more accurate comparisons with later studies.

Further to the study by Palareti et al. (1996), a prospective cohort study conducted by Panneerselvam et al. (1998) in Cambridge, England, attempted to determine risk factors for over-anticoagulation in patients receiving long-term warfarin therapy. This study was important because the authors were the first to believe that identification of risk factors would allow pre-emptive dose reductions and intensification of monitoring, which could potentially reduce bleeding complications. Unlike previous studies that had been limited to the identification of bleeding associated with high INR values, the authors of this study prospectively identified those risk factors associated with the development of a high INR in patients that fell into the high-risk category for bleeding complications. Thus, for the first time, episodes of over-anticoagulation could be potentially preventable. During a 12-month period, prospective monitoring identified all INRs>7.0. This value was chosen on the basis that the previous study by Palareti et al. (1996) had identified a significant increase in the bleeding risk of patients with an INR>7.0. The authors concluded that patients with a target INR of 3.5 were more likely to become over-anticoagulated and more likely to bleed than patients with a target of 2.5. All patients with a target INR of 3.5 had mechanical heart valve prostheses and patients with a target INR of 2.5 had AF. The second-highest risk factor for a patient to develop a high INR was found to be a change in medication, especially the administration of antibiotic therapy in the four weeks prior to a high INR. The third risk factor for developing a high INR was identified as the presence of an intercurrent infection. It was recommended that when a patient had

developed an intercurrent illness and was prescribed antibiotics, there was a clear risk factor for over-anticoagulation present and it was recommended that a pre-emptive dose adjustment and/or more frequent monitoring of the INR was required. Those patients with an INR>7.0 were not found to be significantly older, but the authors concluded that the sample size (n=31) may have been too small to detect a significant difference. A possible explanation for the age factor may have been that older patients with a high INR are more likely to bleed than younger patients with a similar degree of over-anticoagulation, but age alone does not necessarily increase the risk for over-anticoagulation (Panneerselvam et al. 1998). Thus, the risk factors identified in order of importance were a target INR of 3.5 or more, a change in medication, the administration of an antibiotic and the development of an intercurrent illness (Panneerselvam et al. 1998).

Results from these studies had potentially identified several risk factors for major bleeds. While the advancing age of the patient remained controversial and inconclusive, such factors as the intensity of anticoagulant therapy, a shorter duration of therapy and a greater variation and instability in the INR values were all considered to be potential risk factors for a major bleed. Moreover, the presence of a 'front loading' of bleeds during the initial three months of therapy was commonly observed, but the exact reasons for this remained unclear. It was considered that a local bleeding source in the form of a lesion or tumour unmasked by the warfarin therapy may be the primary reason, although the possibility that patients were often less well controlled at the start of therapy due to changes in their warfarin doses, the discontinuity of care and factors that affect warfarin metabolism may have also contributed. The frequency of INR monitoring was not detailed in any of the studies, thus it was not possible to exclude the possibility that a lack of INR monitoring may have led to high INRs. Although the presence of certain co-morbid conditions was considered to contribute to the risk for a major bleed, there remained controversy as to which conditions were significant and whether it was the presence of other medications or the presence of the co-morbid condition that contributed to the increased risk.

While many potential risk factors for bleeding had been identified by this time, little was known about how to stratify patients by their individual bleeding risks (Beyth, Quinn & Landefeld 1998). In an attempt to estimate the risk for warfarin-related major bleeds, a cohort study by Beyth, Quinn and Landefeld (1998) evaluated the accuracy and clinical utility of an existing Outpatient Bleeding Risk Index. The authors postulated that by

improving the selection process of patients and identifying those patients who were at a higher risk for a bleed, better use of warfarin could be facilitated. Furthermore, the authors wished to determine the ability of the patient's physician to predict bleeding compared with the index and to determine whether bleeding was potentially preventable in high-risk patients identified by the index. This study appeared to further validate the prospect of being able to identify several risk factors and thus prevent episodes of over-anticoagulation with conscientious management and frequent monitoring rather than excluding high-risk patients from warfarin therapy.

The results from the validation sample of 264 outpatients discharged from university hospitals in Cleveland between April 1986 and April 1987 commencing on warfarin therapy were compared with a previous cohort of 556 patients assessed when the index was derived. The derivation cohort was assembled from patients discharged from Brigham and Women's Hospital, Boston, Massachusetts, between 1977 and 1983.

Physicians prescribing warfarin for each patient in the validation sample of 264 patients were asked to 'estimate the probability of major bleeding during anticoagulation as an outpatient' (Beyth, Quinn & Landefeld 1998:92). Estimates included both qualitative categories, i.e. very high, high, middle, low or very low probability of bleeding, and continuous data ranging from a 0-100% rating. Warfarin effect was expressed in terms of the INR. The Outpatient Bleeding Risk Index classified patients into three groups by predicted cumulative risk of major bleeding. Low-risk patients were identified as having no risk factors, intermediate-risk patients as having one or two risk factors and high-risk patients as having three or four risk factors. Four risk factors were identified as being independently related to major bleeding: patients older than 65 years, a history of gastrointestinal bleeding, a history of stroke and the presence of one or more of the following co-morbid conditions: recent myocardial infarction, renal insufficiency, severe anaemia at discharge or diabetes mellitus. The prediction rule ably predicted those at the highest risk of bleeding events in the validation sample at 6, 12 and 48 months (Beyth, Quinn & Landefeld 1998).

Results indicated that the rate of a major bleed was 7% per year of therapy in the derivation group in Boston compared with a rate of 5% per year of therapy in the validation group in Cleveland, indicating that the difference between the two groups was not statistically significant (P=0.11). However, the results indicated that bleeding after the initial 6 months was to some extent less frequent, again suggesting the presence of a

'front loading' of bleeds during the initial months of therapy. Of the comparison of the Outpatient Bleeding Risk Index to physicians' ability to estimate the probability of a major bleed, the physicians' estimates were not found to be associated with the observed frequency of major bleeds. Major bleeding occurred in 10% of patients whom physicians had deemed to be at a 'very low' risk, 12% of patients deemed to be at a 'low' risk and 4% of patients deemed to be at a 'middle' or 'very high' risk of bleeding. Overall, the physicians did not estimate the probability of a major bleed during outpatient warfarin therapy any better than would be expected by chance and in fact were often inaccurate. One of the reasons why the estimation rate of the number of patients were deemed to be 'very low' or 'low' risk may have been because the physicians in the study had already decided to start warfarin therapy and any patients who were considered to be at an excessive risk of a bleed would have already been eliminated from the study.

Most importantly, the study found that the Outpatient Bleeding Risk Index identified many patients as 'high risk' who subsequently developed a major haemorrhage. These major bleeds may well have been avoided had the risk factors been identified and warfarin management more closely monitored. Overall, the findings of the study indicated that physicians' estimates could be improved by using the Outpatient Bleeding Risk Index in the initial assessment in conjunction with other assessments, such as the patient's cognitive and functional status and likelihood of compliance with therapy determine which patients might require more intense monitoring. Thus, it was concluded by the authors that inaccurate estimates of bleeding risks might lead to inappropriate and inadequate management of these high-risk patients (Beyth, Quinn & Landefeld 1998).

Conversely, a retrospective medical record review by Wittkowsky and Devine (2004) conducted in Washington, US, involving 1,020 patients, and attempting to determine the frequency and cause of over- and under-anticoagulation in patients treated with warfarin therapy, found that although out-of-range INRs were frequently encountered during warfarin therapy, the specific causes were commonly not identified. Of the 603 INRs>4.0, the cause of 43.0% of these was not clearly identified. Other causes of over-anticoagulation were identified as changes in the patient's medical condition (15.9%), response to a previous change in the warfarin dose (11.4%), interaction with prescribed drugs (7.3%) and other factors, such as non-compliance or dosing errors, initiation of therapy, changes in dietary vitamin K intake, accounted for 15.4%. The authors did observe that even though guidelines for the management of warfarin therapy were

followed, only 51.5% of patients were in the target range. Importantly, results showed that major bleeding was more likely to occur when there was an episode of over-anticoagulation, thus substantiating the importance of maintaining the INR within the target range (Wittkowsky & Devine 2004).

Although the study does not detail frequency of INR monitoring, the authors stated that 'all patients were treated according to internal standards of practice developed in accordance with current consensus guidelines for the management of warfarin therapy' (Wittkowsky & Devine 2004:1312). As the consensus guidelines do not stipulate the exact frequency of INR monitoring to be undertaken, but rather are a guideline as to the recommended frequency, it is possible for one patient to undergo INR monitoring as little as 7 times per month in the first month of treatment and another patient to undergo monitoring as many as 16-20 times. The frequency of monitoring is left up to the discretion of the treating physician. This would indicate that the real frequency of monitoring that occurred during the study was unknown as to whether it was sufficient or not. The results of the study indicate that while it may not be possible to identify the specific cause of over-anticoagulation, prevention of over-anticoagulation itself might reduce the likelihood of a major bleed (Wittkowsky & Devine 2004). Whether or not more frequent monitoring of INRs and careful management would avert these incidences was not known.

On the other hand, the authors of a retrospective review of over-anticoagulated patients with an INR above or equal to 6.0 in Canada were able to identify the likely cause of excessive anticoagulation in 68% of cases (Brigden et al. 1998). That is, only 32% of the causes of over-anticoagulation could not be identified as opposed to 43% by Wittkowsky and Devine (2004). The authors identified drug interactions followed by compliance issues as the two most frequent causes of over-anticoagulation (Brigden et al. 1998). If one were to assume that these statistics are accurate, they would indicate that the majority of episodes of over-anticoagulation were potentially preventable. That is, if consensus guidelines were followed by the clinicians and compliance by patients was of a high standard, it would seem highly probable that more patients would have been within the target range. This will be further explored in this study.

In assessing the factors associated with increased bleeding risks and warfarin therapy, it is essential to determine the effect of excessive anticoagulation on the mortality and morbidity of these patients. A study by Koo et al. (2004), conducted in the Brigham and

Women's Hospital in Boston, Massachusetts. found that the mortality of patients who had experienced a major bleed and had excessive anticoagulation was greater than if patients had experienced a major bleed but had no excessive anticoagulation. The authors of this study identified 101 consecutive in-patients with major anticoagulated bleeding according to the Landefeld Bleeding Severity Index (Landefeld et al. 1989), during administration of warfarin, unfractionated heparin or low-molecular-weight heparin over a period of two months. Among the cohort, 50 patients had excessive levels of anticoagulation and 51 did not. Of the patients receiving warfarin, excessive therapy was associated with an increased mortality rate at 60 days. That is, six patients or 21% with excessive anticoagulation versus nil with no excessive anticoagulation (P=0.49) died. Excessive anticoagulation remained a significant predictor of mortality even after controlling for other clinical factors (P=0.01), as were intracranial haemorrhage (P=0.005) and active malignancy (P=0.03). Excessive anticoagulation for patients receiving warfarin was defined as an INR above the intended therapeutic range. Furthermore, the results of the study were consistent with those of the study by Hylek and Singer (1994) in determining that even though excessive anticoagulation increased the risk of intracranial haemorrhage, it may occur when the INR is within the target range. Koo et al. (2004) found that nine (69%) of the thirteen patients with no excessive anticoagulation had intracranial bleeds. Most importantly, the authors of this study concluded that the main cause of excessive anticoagulation in their study was attributed to 'errors in drug monitoring' (Koo et al. 2004:1560). While the details of the errors in drug monitoring were not disclosed, one can only assume that there was a problem in the frequency of monitoring, suggesting that closer monitoring may aid in preventing episodes of over-anticoagulation and the resultant magnitude of adverse clinical outcomes.

It is important for clinicians to be able to determine the consequences of anticoagulant-related bleeding and weigh the risks and benefits of extended-duration anticoagulation. A meta-analysis conducted by Linkins, Choi & Douketis (2003) attempted to provide reliable estimates of the risk and clinical impact of bleeding in patients taking oral anticoagulants for venous thromboembolism. Only randomised, controlled trials and prospective cohort studies that followed patients for at least three months with a target INR of 2.0-3.0 and conducted between 1989 and 2003 were included in the review. Bleeding was defined as the case-fatality rate of major bleeding and the risk for intracranial bleeding. Of the 10,757 patients included in the analysis, major bleeding

occurred at a rate of 7.22 per 100 patient-years (95% CI, 7.9-7.24), fatal bleeding at a rate of 1.31 per 100 patient-years (95% CI, 1.30-1.32) and intracranial bleeding at a rate of 1.15 per 100 patient-years (CI, 1.14-1.16). Intracranial bleeds accounted for 8.7% of all major bleeding episodes and of the 24 intracranial bleeds, 11 were fatal. Overall, of the 276 episodes of major bleeds, 37 were fatal, indicating that the case-fatality rate for a major bleed was 13.4% (CI, 9.4-17.4%). The interpretation of these results indicates that the clinical impact of anticoagulant-related major bleeding means that approximately one in seven bleeding episodes is fatal or intracranial. This is a considerable risk and according to the authors, may be greater than previously perceived (Linkins, Choi & Douketis 2003).

Most importantly, after the initial three months of anticoagulant therapy, the case-fatality rate for a major bleed was reduced to 9.1% and the risk for an intracranial bleed was 0.65 per 100 patient-years in patients who received extended-duration anticoagulation. The authors found a 'front loading' of major bleeding episodes very soon after the initiation of therapy, that is, as many major bleeds occurred during the first three months of therapy as during the entire year after this period. The authors determined that this was consistent with the hypothesis that patients with an underlying predisposition to experience a bleed were more likely to do so soon after therapy began. The results of this analysis are likely to be robust and valid because only studies that used the INR to monitor the intensity of the anticoagulant therapy and well-designed randomised clinical and prospective trials were included in the meta-analysis (Linkins, Choi & Douketis 2003).

In summary, while bleeding is the most common complication of warfarin therapy and previous studies (Palareti et al. 1996; Rosand et al. 2004) have shown that the risk of bleeding rises exponentially as the INR rises, 50% of bleeding episodes occur when the INR<4.0 (Campbell et al. 2001). Additionally, the patient is thought to be at the greatest risk of incurring a bleed during the first three months of therapy (Landefeld & Beyth 1993; Linkins, Choi & Douketis 2003). Hence, two of the objectives of this study are to assess the rate of episodes of over-anticoagulation during the initial five months of therapy, specifically the rate in the first month compared with subsequent months, and to assess the number of major bleeds associated with those episodes of over-anticoagulation. The number of major bleeds not associated with an episode of over-anticoagulation will also be determined. The third objective that has been previously addressed is the number of episodes of over-anticoagulation that were potentially preventable and the number that

were unforeseeable. In addition, the study will determine if a lack of INR monitoring leads to an increased number of episodes of over-anticoagulation.

This chapter has critically examined the literature pertaining to the study objectives, that is, the frequent observation of a 'front loading' of excessive anticoagulation during the initial few months of therapy, the association between high INR values and major bleeds and the potential for clinicians to foresee an unstable INR and thus increase the frequency of monitoring, particularly during the initial month of warfarin therapy. Thus far, the literature review has provided a background to known increased risk factors associated with bleeding complications during warfarin therapy, which has revealed the need for further clarification.

2.5 Drug interactions

Three unfavourable properties of high protein binding, cytochrome P450-dependent metabolism and a narrow therapeutic index are combined in warfarin and as a result a list of drugs of approximately 250 compounds that may potentially interact with warfarin have been listed (Harder & Thurmann 1996). Because of the ever expanding list of drugs that may potentially interact with warfarin, it is impossible to discuss them all in detail here and thus, for the purpose of this study, only those agents with documented interactions and those commonly prescribed and considered to increase the effect of warfarin will be mentioned. Noteworthy of mention are antiplatelets, such as aspirin, clopidogrel, dipyridamole and ticlopidine, statins, nonsteroidal anti-inflammatory drugs (NSAIDS) such as ibuprofen, some antibiotics, anticonvulsants, antilipidaemics, selective serotonin re-uptake inhibitors (SSRIs) and antiarrhythmics such as amiodarone. Anticoagulants such as heparin and low molecular weight heparin, antifungals, analgesics such as paracetamol, and gastrointestinal agents will be discussed briefly.

In most incidences of drug interactions with warfarin, there is either an inhibition or increased effect of warfarin metabolism (Horton & Bushwick 1999). According to Horton and Bushwick (1999), medications used for the management of chronic diseases are controllable, but difficulty arises in the management of interactions when medications are used for short-term indications. Panneerselvam et al. (1998) found in their study that a recent change in medication was one of the most common precipitants associated with an episode of over-anticoagulation. Glasheen (2005) postulates that since many medications

may have some effect on warfarin's anticoagulant effect, it is prudent to cast a cautious eye on any drug before introducing it into a warfarin regimen.

While the combination of warfarin and antiplatelet drugs are not commonly recommended, there are situations in which this combination is deliberately used (Ho & Brighton 2002). The warfarin-antiplatelet combination is reported to increase the risk of both major and minor bleeding by increasing the effects of platelet function, interfering with warfarin metabolism which produces an increase in the INR and via unique adverse effect profiles such as gastrointestinal tract erosions with aspirins and non-steroidal anti-inflammatory drugs (Ho & Brighton 2002). In fact, the concurrent use of warfarin and NSAIDS in the elderly population has been estimated to cause a 13-fold increase in the risk of upper gastrointestinal tract bleeding (Shorr et al. 1993). Additionally, increased bleeding risks have been reported with combined warfarin-aspirin therapy in studies involving patients post-infarction with an INR target of 2.5 (Hurlen et al. 2002; van Es et al. 2002). When high doses of aspirin are taken during high-intensity warfarin therapy, that is, when the INR target is set to 3.0-4.5, the risk of clinically important bleeding is increased (Dale, Myhre & Loew 1980).

It has been reported that approximately 20% of AF patients receiving warfarin therapy also receive antiplatelet therapy for the treatment of coronary heart disease or cerebrovascular disease (Howard et al. 2002). Additionally, the study by Howard et al. (2002), conducted in Kansas and involving the retrospective examination of the medical records of 704 Medicare beneficiaries aged over 65 years with AF and discharged from hospital after being initiated on warfarin therapy, reported that 54% of them were prescribed another medication that would increase the bleeding risk. Of those drugs prescribed, antibiotics accounted for 67% and aspirin for 61% of the 21% of patients who received prescriptions for drugs, which could inhibit haemostasis (Howard et al. 2002).

Shireman et al. (2004:2362) reported that 'the impact of combined warfarin-antiplatelet therapy on bleeding risks remains unclear because of inconsistencies between randomised trial designs and clinical practice'. These inconsistencies included exclusion of elderly patients and those patients with known bleeding risks from clinical trials and the use of lower warfarin doses than would be commonly used in clinical practice. In a retrospective cohort analysis conducted in Kansas, US, involving 10,093 cases, Shireman et al. (2004) attempted to examine the potential impact of combined therapy on major bleeding risks. The results of the study conflicted with the results of The Stroke Prevention in Atrial

Fibrillation Investigators (1996) and the clinical trial conducted by Gullov, Koefoed and Peterson (1999), where both studies reported that no additional risks with combined therapy were present. The results of the study by Shireman et al. (2004) indicated that after accounting for other risk factors, combined warfarin-antiplatelet therapy increased the risk for a major bleed by 50% during the 90-day follow-up period. Major bleeding events occurred in 1.3% of the patients receiving warfarin only and in 1.9% (P =0.052) of the patients receiving combined warfarin-antiplatelet therapy (OR, 1.46; 95% CI, 0.998-2.12) (Shireman et al. 2004).

Results also indicated that other factors that may expose patients to a higher bleeding risk included anaemia (OR, 2.52; 95% CI, 1.64-3.88), age (OR, 1.03; 95% CI, 1.002-1.05) and a previous bleeding history (OR, 2.40; 95% CI, 1.71-3.38). However, the authors could not rule out that unknown factors may have played a role in contributing to the increased risk, such as the presence of cerebral vascular disease (Shireman et al. 2004). Because bleeding is most likely to occur during the first three months of treatment (Gallus et al. 2000), and because almost 40% of the study population had been on warfarin prior to admission, the effects of treatment duration were unable to be determined. The most alarming concern of the study results was the finding of a 3-fold increase in the risk of intracerebral haemorrhage with combined therapy over time of 0.9% versus 0.3% at 180 days. Although the results of the study indicate that combined therapy increased the risk of bleeding, it was determined that it was a moderate increase in risk only. While the authors acknowledged several limitations to their study, they recommended that it would be advantageous for physicians to remain cautious when considering the combination of warfarin and antiplatelet therapy and to evaluate the risk:benefit ratio of combined therapy until such a time as a conclusive outcome was determined (Shireman et al. 2004).

Because NSAIDS, including aspirin, have been reported to increase the risk of bleeds (Hurlen et al. 2002; van Es et al. 2002) and paracetamol has no antiplatelet effect or potential to induce gastrointestinal bleeding, it is the preferred choice of analgesia and is therefore commonly prescribed (Chan 1995). However, while evidence suggests that patients taking paracetamol and warfarin concurrently may incur an increase in their INR value, this remains a debatable issue. Two studies by Hylek et al. (1998) and Gebauer et al. (2003) reported a significant increase in the INR value after concurrent paracetamol. Hylek et al. (1998) conducted a prospective case-control study at Massachusetts General Hospital, Boston, in an attempt to quantify the effects of several commonly encountered

risk factors for over-anticoagulation. Case patients (n=93) were identified as those with an INR greater than 6.0, reported within 24 hours, whose target INR was 2.0-3.0, and control patients (n=196) were identified as those randomly selected from patients having an INR of 1.7-3.3. Factors associated with the INR greater than 6.0 and evaluated in the study included medication use, recent diet, illness, alcohol consumption and actual warfarin use. Results indicated that paracetamol was independently associated in a dose-dependent manner with having an INR>6.0 (P<0.001). That is, 56% of patients with an elevated INR>6.0 had also been taking paracetamol. For an intake of paracetamol of 9,100 mg/week or more, the odds of having an INR greater than 6.0 was increased 10-fold (95% CI, 2.6-37.9) above those taking no paracetamol. The risk for bleeding decreased with lower intakes of the drug reaching the background level of risk at an intake of 6 or less than 325 mg tablets per week. Other factors found to be independently associated with an INR>6.0 were new medications known to potentiate warfarin, advanced malignancy, recent diarrhoeal illness, decreased oral intake and taking more warfarin than was prescribed (Hylek et al. 1998).

Similarly, Gebauer et al. (2003) reported that a patient who had been stable on warfarin therapy for four years previously had an increase in the INR value of 6.4 from 2.3 after four grams of paracetamol per day for three days. The patient had reported that there were no other changes in his usual routine including diet, drug, alcohol or herbal preparations intake, smoking, compliance with warfarin or recent illness that may have impacted on the INR value (Gebauer et al. 2003).

A limitation in the study by Hylek et al. (1998) was the inability of the researchers to control for confounding factors that may have significantly impacted on the outcome. In fact, Gebauer et al. (2003) suggest that despite the evidence of studies indicating the existence of an interaction between paracetamol and warfarin, there still remains considerable conjecture about the existence of an interaction, predominantly because the interaction is observed inconsistently in clinical practice and a plausible explanation of the mechanism remains unresolved. Thus, this remains an important unresolved clinical issue for the many patients with co-morbidities who require this analgesia and receive warfarin. The authors concluded that it would be prudent of clinicians to advise patients not to exceed 2 grams per day of paracetamol and that more frequent INR monitoring should be conducted if patients begin taking paracetamol at dosages greater than this amount (Gebauer et al. 2003).

The substantial increase in the use of complementary medicines has made the potential for drug interactions an important issue for many clinicians and therefore more definitive information is required regarding the severity, onset and management of these potential interactions (Heck, Dewitt & Lukes 2000). Nearly all data on potential drug interactions between herbal medicines and warfarin are based on in vitro data, animal studies or individual case reports, making it very difficult for doctors to make accurate clinical decisions (Heck, Dewitt & Lukes 2000). The products reported to potentially interact with warfarin and result in an increase in the INR value include herbs with coumarin, salicylate or antiplatelet properties, feverfew, garlic, ginger and ginkgo. The herbal products that have been associated with published case reports of possible interactions with warfarin include danshen, devil's claw, dong quai, green tea, ginseng and papain, and dietary supplements including coenzyme Q and vitamin E (Heck, Dewitt & Lukes 2000).

Interactions between warfarin and various antibiotics with varying clinical significance have also been reported to increase the effect of warfarin by inhibiting metabolism via the cytochrome P450 system or by decreasing bacterial vitamin K production or increasing clearance of vitamin K, although the latter reasoning is reportedly overestimated (Hirsh et al. 2003). Worth mentioning are cotrimoxazole, erythromycin, fluconazole, isoniazid, metronidazole and miconazole (Wiese & Cosh 1999), trimethoprim-sulfamethoxazole (Glasheen 2005) and sulfonamides and several broad-spectrum antibiotics (Udall 1965). Penicillins, especially amoxicillin/clavulonate (Glasheen 2005), in high doses have been reported to increase the risk of bleeding by inhibiting platelet function (Hirsh et al. 2003). Other commonly prescribed drugs reported by Wiese and Cosh (1999) to interact with warfarin are cimetidine, omeprazole, amiodarone, propranolol and phenylbutazone.

Glasheen (2005) suggests that it is nearly impossible to differentiate between the effect of the antibiotic and the effect of the patient's illness in acutely ill patients. Factors associated with acute infections, such as fever, diarrhoea, anorexia and changes in the hepatic and renal function are all understood to impact on the body's response to warfarin. The author emphasises the importance of vigilantly monitoring the INR in any acutely ill patient, especially if they have been commenced on an antibiotic (Glasheen 2005).

Amiodarone, an effective drug in the management of supraventricular and life-threatening ventricular arrhythmias, has been reported as one of the drugs most frequently

encountered to produce drug interactions with warfarin (Kerin et al. 1998; Sanoski & Bauman 2002). Amiodarone has a strong ability to potentiate the anticoagulant effect of warfarin, which results in an increased INR value and resultant increase in the risk of a bleeding event. Unlike the interaction between paracetamol and warfarin, this drug interaction has been described as commonly encountered in clinical practice (Sanoski & Bauman 2002).

In summary, this section has provided a review of the relevant literature pertaining to those drugs that may be considered to potentially interact with warfarin and influence the outcome. In conclusion, because of the complex response and unresolved issues concerning interactions with concurrent medications and warfarin, and the unpredictable degree of effect or occurrence in the outcome, it would appear prudent for clinicians to closely monitor changes in INR values by frequent measurements when adding or deleting virtually any drug or alternative product suspected of causing an interaction with patients receiving warfarin therapy.

2.6 Food interactions

Among the many factors thought to influence the effect of anticoagulation in patients receiving warfarin therapy is the dietary effect of vitamin K. As an objective of this study was to determine the patient's health status and degree of compliance with their warfarin therapy in the period leading up to an episode of over-anticoagulation, it was important to assess whether there were any major changes in their normal eating habits or their alcohol intake during that time.

The effect of daily vitamin K consumption on warfarin anticoagulated patients consuming normal diets long term has not been subjected to numerous systematic studies (Lubetsky et al. 1999), but it is widely accepted that reduced dietary vitamin K intake may potentiate the effect of warfarin in sick patients (Hylek et al. 1998). In particular, those patients treated with antibiotics and intravenous fluids with no added vitamin K supplements and patients who suffer from fat malabsorption states may suffer an increase in INR results (Hirsh et al. 2003).

It is therefore recommended in the approved product information for coumadin that patients receiving warfarin therapy should maintain a consistent, normal balanced diet in order to stabilise their vitamin K intake while receiving therapy (Caswell et al. 2001). The

principal dietary sources rich in vitamin K are spinach, lettuce (particularly those with dark green leaves), broccoli, asparagus, avocadoes, green tea, Brussels sprouts, cauliflower, chick peas, kale, soybean, canola, cottonseed, pork and beef livers and olive oils (Aldrich 1997).

Black (1994) postulated that acute diarrhoeal diseases, including giardiasis, might disturb the equilibrium between vitamin K and warfarin, increasing the risk of bleeding complications. He observed approximately one week after suffering a bout of giardiasis and while receiving warfarin therapy, that his INR was 4.6 while controls had previously been stable between 2.0-3.0. It was thought that the diarrhoea had caused malabsorption of dietary vitamin K, resulting in an excessive effect of anticoagulation. The alternative reasoning for the increased INR value, according to the author, may have been a decreased intake in green vegetables or an interaction with other drugs taken during that period of time (Black 1994). While this has been recorded as a single episode and requires confirmation and further investigation, if this effect is verified, it may cause a substantial impact on patients receiving anticoagulant therapy.

Alcohol intake remains a controversial issue regarding the cause of episodes of increased INR values and has been most frequently reported to have an impact when patients concurrently suffer a liver disease and take in excessive amounts of alcohol (Wells et al. 1994). Additionally, it would appear that heavy drinkers are at an increased risk of falls, alcohol-induced gastritis, poor diet and poor compliance, all of which increase the risk of bleeding. It is thought that small to moderate amounts of alcohol probably have little effect on warfarin metabolism itself (Campbell et al. 2001).

2.7 Effect of genetic factors on warfarin therapy

While this research project will not investigate the effect of genetic factors on warfarin therapy, it has been suggested that an understanding of the genetic factors associated with the individuality of the warfarin dose response ratio, in particular, the interactions that affect oxidation metabolism of either the S- or R-isomer of warfarin, may shed some light on some of the clinical difficulties encountered in maintaining the target INR. Therefore, this section will briefly discuss the existing evidence regarding CYP2C9 gene variants and clinical outcomes in warfarin-treated patients.

Because the S-isomer is five times more potent than the R-isomer as a vitamin K antagonist, it is clinically more important (O'Reilly 1974). Relling et al. (1990) determined that CYP2C9, a hepatic microsomal enzyme in the cytochrome P450 system, was able to catalyse the metabolism of several therapeutic agents. Two years later, Rettie et al. (1992) identified CYP2C9 as the principal enzyme responsible for the conversion of the therapeutically active S-enantiomer of warfarin to its inactive 6-hydroxy and 7-hydroxy metabolites. Additionally, Goldstein and de Morais (1994) revealed that this CYP isoform had several allelic variants associated with altered clearance and rates of metabolism.

Of the several mutant alleles that have been cloned since then, CYP2C9*3 has been identified as having significant pharmacokinetic consequences for the clearance of some drugs such as tolbutamide, losartan (Sullivan-Klose et al. 1996), phenytoin (Veronese et al. 1993) and for substrates that have low therapeutic indices, such as S-warfarin (Steward et al. 1997). In the study by Steward et al. (1997), a patient, who had demonstrated to be unusually sensitive to warfarin therapy and could tolerate no more than 0.5 mg of the drug per day, was genotyped and found to be homozygous for CYP2C9*3. The effect of CYP2C9*3 on S-warfarin was associated with a diminished clearance and a dangerously exacerbated therapeutic response to normal doses of the drug (Steward et al. 1997).

Aithal et al. (1999) also determined that there was a strong association between CYP2C9 variant alleles and low warfarin dose requirements in randomly selected patients who were attending an anticoagulation clinic in Newcastle, UK. In examining the CYP2C9 genetic constitution of an individual, the authors found that a subgroup of patients might be identified that not only have difficulty at induction of warfarin therapy, but also are potentially at a higher risk of bleeding complications. The authors found that of the 20 (56%) of the 36 patients in the low-dose group with their peak INR rising above the target range after a fixed-dose regimen, 18 carried one or more variant CYP2C9 alleles. Furthermore, the incidence of major bleeding complications in this group was four times higher than in patients in the control group (Aithal et al. 1999). It was suggested by the authors that the knowledge of CYP2C9 genotype may help to reduce difficulties during initiation of warfarin therapy and indicated that the likely increased risk of bleeding in patients with genetic mutations may influence the decision to commence warfarin therapy, particularly in patients in whom the benefit was deemed to be small (Aithal et al. 1999). Halkin and Lubetsky (1999), in response to the report by Aithal et al. (1999),

suggested that differences in dietary vitamin K intake, which was not accounted for in the study, might have caused the differences in warfarin sensitivity. Aithal et al. (1999) argued that this was not the case and that the vitamin K intake of patients in their study fell within the range of daily doses and they thought it unlikely that CYP2C9 would play a part in determining dietary vitamin K intake, although they did admit that the clinical implications of assessing daily vitamin K intake were unclear.

The theory that genetic factors may influence the dose response ratio of warfarin is not an isolated theory and several studies have supported the suggestion that an understanding of the genetics and disposition of warfarin metabolism would clearly aid the process of correct dosage (Furuya et al. 1995; Loebstein et al. 2001; Steward et al. 1997). Takahashi and Echizen (2001) also postulated that the genetic polymorphism of CYP2C9 might be associated with a wide inter-patient variability in the hepatic metabolism of the S-enantiomer of warfarin, resulting in an impaired elimination of the drug and a variable anticoagulation response.

In summary, a systematic review and meta-analysis of 11 available studies meeting the review inclusion criteria regarding the strength and quality of existing evidence concerning CYP2C9 gene variants and clinical outcomes in warfarin-treated patients was conducted by Sanderson, Emery and Higgins (2005) in Cambridge, UK. This study was considered to be the first rigorous and systematic review and meta-analysis completed on this topic. The results of the review showed that variant alleles are common in Caucasian warfarin-treated patients, with approximately 20% of patients carrying at least one variant. The review showed consistent and strong evidence to support the suggestion that a lower maintenance dose for patients with either 2C9 variant, with the lowest requirements for patients with 2C9*3, is required. Although the risk of bleeding was approximately doubled for patients with a variant allele in those studies reporting bleeding events, there was insufficient evidence to support a case for genotyping in routine clinical practice at this time. Evidence that a test will lead to improved health outcomes and cost effectiveness of CYP2C9 genotyping compared to current care is required before this will occur. At present there is no evidence to suggest that there have been any properly conducted studies that have addressed these issues for the screening for CYP2C9 polymorphisms in patients being initiated on warfarin (Salem 2005). Sanderson, Emery and Higgins (2005) postulated that it is highly likely that the use of established nomograms and intensive monitoring with pre-emptive appropriate dose adjustments

might be more effective in reducing the risk of adverse events without the need for genotyping.

2.8 Effect of age on warfarin therapy

With the increasing number of elderly people and an increasing range of cardiovascular and thromboembolic disorders for which anticoagulant therapy is required, it is necessary to clarify the safety issues surrounding anticoagulant therapy and the elderly. An over-cautious use of warfarin may deprive a large number of patients of its beneficial effects, while routine use of warfarin irrespective of other considerations may precipitate further morbidity or mortality due to increased risks of bleeding complications (Adams & Gautam 1994). There remain controversial issues as to whether there is an increased risk of bleeding complications associated with increasing age and anticoagulant therapy, whether the elderly population is at an intrinsically greater risk of a bleed or whether the elderly population is at no greater risk than the rest of the population.

An early study conducted by Jick et al. (1968) suggested that elderly patients receiving anticoagulants were more prone to increased bleeding risks. The authors performed a prospective epidemiological study carried out in three different Boston hospitals on 97 consecutive patients receiving heparin who were diagnosed with either pulmonary embolism (PE) or deep venous thrombosis (DVT) to assess efficacy and toxicity of heparin in relation to sex and age. The findings were consistent with those of an earlier study by Kernohan and Todd (1966). The actual cause of the increased risk for bleeding was not established in either study and it has to be noted that both studies examined heparin only, not warfarin, and no other extraneous variables were identified. Additionally, both studies suffered several limitations that may have influenced their outcomes.

A prospective study by Sheperd et al. (1977), attempting to confirm and further elucidate conclusions found in an earlier retrospective study by O'Malley et al. (1977) that patients over 70 years of age required smaller doses of warfarin and thus were more sensitive than younger patients, showed similar outcomes. Additionally, the authors paid particular attention to the mechanism of the altered sensitivity to warfarin. They attempted to determine whether the increased sensitivity resulted from differences in warfarin kinetics or from an intrinsic sensitivity to warfarin. The study, carried out in Dundee, Ireland,

incorporated 13 healthy young and 13 healthy elderly people and the equivalent in rats in the study. Following a single dose of racemic warfarin, the results indicated that although the mean half-life was longer and the plasma clearance slightly lower in the elderly human subjects, the differences were not statistically significant and there was no difference between the apparent volumes of distribution in the two age groups. Duration of response in both groups was similar despite the doses in the elderly group being 41% lower on a weight-related basis, indicating that no difference in pharmacokinetics or binding to plasma proteins was evident. When assessing the relative sensitivity of clotting factor synthesis to warfarin, the elderly group of humans demonstrated a much greater degree of inhibition of vitamin K-dependent factor synthesis than did the younger group (Sheperd et al. 1977).

Sheperd et al. (1977) determined that possible explanations for the above findings might include an alteration in warfarin pharmacokinetics, in particular impaired metabolism in the elderly, although their results would indicate that this is not a major factor due to similar mean plasma warfarin clearance rates for the two groups of both humans and rats. The authors came to the conclusion that the increased effect of warfarin in the elderly population was more likely due to an increased intrinsic sensitivity to warfarin due to a decreased affinity of the system for vitamin K and an increased affinity for warfarin. Furthermore, it was thought that elderly subjects were more likely to be deficient in vitamin K due to a reduced dietary intake, defective absorption or alteration in the pharmacokinetics of vitamin K (Sheperd et al. 1977).

The earlier study by O'Malley et al. (1977) did not take into consideration the length of time the subjects had been on warfarin therapy. Some subjects had been on long-term therapy, while others had only recently been commenced on treatment. This may have influenced the outcome of the overall sensitivity of the elderly patients to the warfarin dosages as recent research indicates that patients are at the greatest risk of bleeding and experience unstable INR results in the first few months of commencing treatment (Campbell et al. 2001; Vadher, Patterson & Leaning 1997). The sample size in the study by Sheperd et al. (1977) was small, thus limiting generalisability. Furthermore, the study did not exclude any confounding factors with other factors that may be associated with age itself. However, even though patients in the study were not receiving other drugs known or thought to interfere with warfarin effects, a greater sensitivity to warfarin was still observed (Sheperd et al. 1977).

A survey by Dobrzanski et al. (1983), carried out on a random sample of 100 male and female patients attending anticoagulant clinics in West Yorkshire, UK, focused on a possible link between warfarin dosage and age and weight. Data were recorded regarding the age, weight and dose prescribed for patients already with a prothrombin ratio of between 2-3. Patients on those drugs known to interact with warfarin were excluded from the study. Results of linear regression analysis indicated that there was a significant correlation between age and maintenance dose ($r = -0.39$; $P<0.001$), and weight and maintenance dose ($r = 0.39$; $P<0.001$), but that there was no significant correlation between age and weight ($r = -0.17$). When multiple regression analysis was used, a relationship between age and weight together and the maintenance dose of warfarin was significant. The authors confirmed that a patient's requirements for warfarin decreased with age and that they increased with increasing weight, but that age and weight were not the only factors to be considered. They also concluded that attention to a patient's age and weight may be more important to the clinician prescribing the warfarin dose when considering the initiation of the drug, as opposed to the maintenance dose (Dobrzanski et al. 1983).

A study by Redwood et al. (1991) attempted to clarify the shortfalls of earlier studies by assessing two groups of patients. The study was conducted in an anticoagulation clinic at St Mary's Hospital, London. The first group consisted of 364 patients aged between 23-89 years attending a single anticoagulation clinic who had demonstrated a stable anticoagulant effect on medium or long-term warfarin therapy. The second group consisted of 130 patients aged between 15-83 years who were attending the hospital and were being anticoagulated with the standard protocol in use. Results were expressed as an INR. The aim of the study was to establish the extent of dose reduction required in elderly patients on medium to long-term therapy if the same degree of anticoagulation was to be achieved as in younger patients and to determine whether elderly patients showed any greater effect when a standard initial dose of warfarin was prescribed. This had not been clarified in previous studies.

Results of the study confirmed earlier findings that elderly patients on average were more sensitive to the effects of warfarin therapy, but the reasons remained unknown. Additionally, there was no relationship found between age and the intensity of anticoagulation (Redwood et al. 1991). The authors estimated that by the time a patient had reached 70 years, the dose requirement had fallen by a quarter to one third. This was

estimated in a comparison with a 30-year-old patient, but variations in doses required to reach an anticoagulant effect between different subjects of the same age was such that they could not predict an accurate dose reliably. In contrast to the study by Sheperd et al. (1977), the authors of this study did not find any significant relationship between age and the INR in patients receiving a fixed initial dose of warfarin and they postulated that other factors contributed to variations in anticoagulant effect between individuals rather than age. They also determined that because the elderly patients in their study showed no excessive effect from an initial standard warfarin dose, they could be safely initiated on the same variable dose regimens as younger patients, but that they required a lower dose once maintenance therapy was established (Redwood et al. 1991).

In contrast to these earlier studies, a study by Fihn et al. (1993) found that there was no increased risk in bleeding complications with older age, in and of itself, during anticoagulant therapy and the authors suggested that warfarin therapy could be safely administered to the elderly population. The authors of this study claimed that the relevance of previous studies had been jeopardised by the lack of patients drawn from typical practice settings and studies may have yielded conflicting results due to discrepancies in small sample sizes, unique attributes of a single institution's referral base and practice patterns and fluctuations in how complications may have been described. The retrospective cohort study included 928 consecutive patients receiving 1,103 courses of warfarin and was carried out in five institutions in America. The authors set out to test new strategies for the management of warfarin therapy and to determine risk factors for complications that occur during warfarin treatment (Fihn et al. 1993).

Results of the study indicated that, of the many variables examined, four demonstrated an independent relation to risks for bleeding, but when, in a meta-analysis, several studies of the relation between age and the incidence of bleeding were re-analysed, age was not a significant factor. In determining the above, the authors acknowledged that their study suffered from several limitations. The study was retrospective and thus dependent on medical records that were occasionally incomplete, and patient compliance was not accurately recorded, as were the patients' alcohol intake and the severity of complications. Additionally, four of the participating clinics did not report INR values during the first several years, rendering prothrombin time ratios incomparable plus the power of subgroup analyses was limited (Fihn et al. 1993). These limitations would signal caution in the interpretation and recommendations made by this study.

The definition of what constituted a major haemorrhage, the methods of measuring the level of anticoagulation and the target range set may well have all varied among the earlier studies, limiting the validity and generalisability of the outcomes. Additionally, the definition of 'elderly' in most of the studies was being over 60 or 65 and the 'over-60s' group, according to Adams and Gautam (1994), are by no means a homogeneous group, with people in their 60s frequently having more in common with the 'middle-aged' rather than the elderly. Additionally, Hirsh (1987) postulated that earlier studies, because of their use of excessive warfarin dosage to patients, may have been irrelevant and produced inaccurate results.

Because the role of age in warfarin therapy was less than clear and there remained discrepancies in the dosage, McCrory et al. (1995) attempted to determine whether a patient's age affected a physician's decision to use oral anticoagulants or the intensity of the therapy received in patients with nonvalvular AF. The authors surveyed 1,189 randomly selected practitioners across America, using a questionnaire to measure attitudes and beliefs regarding risks associated with anticoagulants, the likelihood of using anticoagulants and the target intensity of anticoagulation of three patient ages and four clinical scenarios. The overall response rate was 38% and results indicated that physicians were less likely to recommend warfarin therapy for the elderly population and less likely to prescribe as intense therapy. McCrory et al. (1995) conceded that it was impossible to tell whether the reported tendency to evade anticoagulation in the elderly was appropriate or not, but that there was a substantial difference in the variation in clinical practice of providing anticoagulant therapy for the elderly patient.

Several studies conducted during 1996 failed to clarify the age: warfarin therapy issues (Fihn et al. 1996; van der Meer et al. 1996; Wynne et al. 1996). Wynne et al. (1996) and van der Meer et al. (1996) determined that there was a significant correlation between age and dosage requirements and that age and achieved INR were the most important and consistent risk factors for bleeding complications. Conversely, Fihn et al. (1996) found that age was not an important determinant of risk for bleeding complications in patients receiving warfarin, with the possible exception of patients over the age of 80 years. These authors proposed that the intensity of warfarin therapy and the deviation in the prothrombin time ratio were much stronger predictors of risks for bleeding (Fihn et al. 1996).

The findings of a study by Palareti et al. (2000), conducted in several anticoagulant clinics in Italy to determine whether elderly patients receiving oral anticoagulant therapy are in fact at an increased risk of bleeding complications, were in line with the results of the study by Fihn et al. (1996). The comprehensive study included 461 patients aged 75 years and older, and 461 patients aged 70 years and younger. The control group of patients aged 70 years and younger were matched for sex. Results indicated a non-significant higher bleeding rate in the elderly group, but moderate anticoagulation with an INR between 2.0-3.0 in the elderly population was apparently the safest and most effective, although there was still a high rate of bleeding in elderly patients with an INR below this range which could not be explained. Additionally, those elderly patients receiving warfarin for arterial vascular disease had a significantly higher incidence of bleeding than the others (Palareti et al. 2000). The authors of the study also determined that conditions requiring oral anticoagulant therapy in the older population are frequent, that is, that 30% of patients starting oral anticoagulant therapy were 70 years or older, thus indicating that there was an urgent need to further clarify the unresolved issues of increased bleeding risks in this age group.

While it was now generally acknowledged that particular care was required when treating elderly patients receiving warfarin therapy in order to avoid bleeding risks, age had been found to be a significant risk factor for bleeding complications in only approximately half of the many studies conducted (McCrory et al. 1995). This would appear to be more than one would expect if related by chance alone, but as previously mentioned, these results may be explained to some extent by other confounding factors associated with age. Additionally, those studies that had observed an increased sensitivity to warfarin with increased age were no closer to determining the cause of the sensitivity. The common thoughts that were beginning to emerge from the above studies were that factors other than age alone should be considered when managing patients on warfarin therapy. The safety of warfarin therapy, particularly in the older age group, was dependent on such factors as close monitoring and a well-controlled INR, the elimination of polypharmacy, the mobility and level of confusion of the patient and the absence of multiple pathology (Adams & Gautam 1994).

Jacobs (2003) presented guidelines abstracted from those developed by the Sixth American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic Therapy (2001) and adapted them for use in the elderly population in an attempt to

overcome the reluctance of many physicians to prescribe oral anticoagulants to the elderly population. Important aspects of the initiation and monitoring of elderly patients receiving warfarin therapy were outlined in the guidelines. It was suggested that a baseline INR should be obtained prior to the commencement of warfarin therapy and the initial dose should approximate the average maintenance dose, usually less than 5 mg daily (Jacobs 2003). Additionally, an evaluation of potential drug, food and disease interactions, including use of other medications, over-the-counter and herbal medications, diet and dietary supplements and stress and fever should be determined. Furthermore, more frequent monitoring of INR values was suggested in the elderly population because of the increased incidence of fluctuations due to illness and alterations in their medication regimes (Jacobs 2003).

Despite well-established documentation of the value of oral anticoagulant therapy in the prevention of thromboembolic complications (Hart et al. 1999) and the above recommended guidelines, many older patients, particularly those with nonvalvular AF, do not receive anticoagulant therapy or receive an inappropriate quality of anticoagulant therapy (Bungard et al. 2000; Johnston et al. 2003).

Kagansky et al. (2004) conducted a combined retrospective and prospective cohort study in the Kaplan-Harzfeld Medical Center in Israel with the aim of clarifying the incidence of bleeding complications and associated risk factors in a large heterogeneous group of older patients receiving warfarin therapy. The study included 323 patients who were 80 years of age or older and discharged on warfarin therapy. The rate of bleeding events, an evaluation of risk factors for bleeding complications and the quality of anticoagulant therapy and monitoring were compared and analysed across a broad range of demographic and clinical variables including cognitive and functional status. All subjects were reviewed for multiple variables that included age, sex, previously known illnesses, concomitant medications, weight and height to calculate body mass index and blood analysis. A pre-designed questionnaire was utilised to evaluate patient socioeconomic and educational levels and an additional questionnaire was utilised to assess the overall knowledge and the impression of the patient or the caregiver on the quality of the relevant education received from the medical system. Additionally, the review of hospital records, telephone interviews with the patient or the caregiver and recording of INR measurements in the community for 310 of the patients were followed up for 28.8±36.3 months.

Demographic details and clinical characteristics indicated most of the subjects were single, had a low income, low educational levels, experienced visual, cognitive and hearing impairments of some degree, and polypharmacy and the existence of co-morbidities were common findings. Almost half of the subjects were 85 years of age or older with the majority consisting of females (61.9%) (Kagansky et al. 2004).

Results indicated that the rates of minor and major bleeding did not increase significantly with increasing age and that warfarin was safe to administer in this elderly group of patients. Even though medications known to interfere with warfarin metabolism were recorded, the use of calcium channel blockers only was associated with a significantly higher rate of minor bleeding complications (P=0.04). However, the study did find that polypharmacy was associated with increased bleeding overall. Those patients who developed a major bleed had a mean ±SD of 37.1%±32.7% of all INR results above the therapeutic range, compared with 15.4% ±17.2% in those patients who did not develop a major bleed (P=0.008). Furthermore, in patients who did not develop a major bleed, there were a significantly higher percentage of INR values below the therapeutic range. While functional and cognitive deficiencies were common, they were not considered significant risk factors for bleeding complications and compliance was reportedly high despite these deficits, thus, according to the authors, the application of antithrombotic therapy could safely be expanded to this group of patients (Kagansky et al. 2004).

Interestingly, only 21.3% of the patients rated the education they received regarding their warfarin therapy as satisfactory, with 61.1% declaring that they did not receive any education at all. There was found to be a significantly strong correlation between the rate of major bleeding complications and insufficient education: 5.2 bleeding events per 1,000 patient-months (P<0.005) among patients who had received insufficient education as opposed to 1.1 bleeding events among patients who did not receive any explanation at all and 0.5 bleeding events among patients who received a satisfactory explanation (P<0.001). There were more INR values below the therapeutic range among those patients who did not receive any information (P<0.001) and the percentage of INR values in the therapeutic range was higher among those patients who received a satisfactory level of education (Kagansky et al. 2004).

My review of the study showed that even though most of the subjects were over 85 years of age, heterogeneous and associated with multiple variables considered potential risk factors for bleeding, the rate of bleeding complications in these frail older patients

receiving warfarin therapy was reported as low. The authors postulated that the bleeding complications could be reduced further by quality patient education provided by medical personnel and maintaining the INR within the therapeutic range and close monitoring of the INR. The quality of education given to the patient or the caregivers was found to be one of the most significant findings in the study and was the most reliable risk factor for increased risk of bleeding complications and the ineffectiveness of oral anticoagulant therapy (Kagansky et al. 2004).

The findings of this study can be considered robust due to the large sample size of older high-risk patients, the detailed functional and cognitive examination of patients and the inclusion of a heterogeneous group, which allowed the authors to evaluate the role of multiple variables in bleeding events. As a result of these strengths, the findings of this study could have significant implications in the clinical setting, indicating that an emphasis on improved oral anticoagulant therapy education may further reduce bleeding complications, particularly in the older group of patients, thus reducing the reluctance of physicians to prescribe warfarin therapy appropriately (Kagansky et al. 2004).

There would appear to be limited published data available pertaining to patients over the age of 80 years receiving warfarin therapy and their daily dose requirements. Garcia et al. (2005), in a prospective cohort study and retrospective cohort secondary data source included 2,359 patients 80 years of age or over in an overall sample size of 12,202 patients from 101 sites in 38 states in the US in an attempt to determine maintenance dose requirements for patients receiving warfarin. The authors found that a significant association between warfarin dose and age and warfarin dose and gender existed. It was found that for each additional year of age, the weekly dose declined by 0.4 mg (95% CI, 0.37-0.44; $P<0.001$) and at any given age, the mean weekly dose for women was 4.5 mg less than that for men (95% CI, 3.8-5.3; $P<0.001$). The study found that women diagnosed with atrial fibrillation and being 80 years of age or more required a median daily dose of 3.1 mg and those diagnosed with venous thromboembolic disease required a median daily dose of 3.6 mg. It was suggested that the recommended daily starting dose of 5 mg would be excessive for up to 82% of women and 65% of men who were more than 70 years of age. The authors postulated that this aggressive dosing in part might explain the higher rates of bleeding and erratic INR values that have been reported during the early stages of warfarin therapy in several previous studies (Hylek & Singer 1994; Landefeld & Goldman 1989; Palareti et al. 1996). It was recommended that lower

initiation and maintenance doses should be considered for the elderly, with older women requiring the lowest doses (Garcia et al. 2005).

According to Garcia et al. (2005), the exact mechanism for increased sensitivity to warfarin with increasing age is still not well understood. Wynne et al. (1995), in Britain, attempted to clarify the reasons for increased sensitivity to warfarin in the elderly population by testing the hypothesis that a fall in hepatic mass with age contributed to the increased sensitivity. In a small sample size of 39 healthy volunteers who were between the ages of 50-87 years, and were stabilised on warfarin for prophylaxis of thrombo-embolism, the authors found a significant negative correlation between liver volume and age ($r = -0.41$; $P = 0.01$), and age and dose ($r = -0.53$; $P = <0.001$), and a positive correlation between liver volume and dose ($r = 0.49$; $P = 0.002$). Results of the study suggested that age and liver volume together accounted for approximately 34% of the variation in warfarin dosing requirements. In interpreting these results, the authors postulated that the increase in sensitivity to warfarin might be due in part to a fall in absolute content of the warfarin receptor vitamin K epoxide reductase, corresponding to the fall in hepatic mass with age (Wynne et al. 1995).

According to Hammerlein, Derendorf and Lowenthal (1998), age-related changes in pharmacokinetics primarily affect drug absorption, distribution, metabolism and elimination, but pharmacodynamic changes in the elderly are only beginning to be understood. According to the authors, it would appear that there has been a paucity of research in this area of geriatric clinical pharmacology and consequently remains an area of continued investigation. Hammerlein, Derendorf and Lowenthal (1998) suggest that a common pharmacokinetic change is reduced drug clearance, which is often associated with the elderly population and pharmacodynamic changes in the elderly can result in a greater or lesser drug sensitivity than that seen in the younger population.

Durnas, Loi and Cusack (1990) had postulated earlier that although there is substantial variation in the effect of age on drug biotransformation, the metabolising of many drugs is impaired in the elderly population. Such factors as a reduction in liver mass, changes in hepatic metabolising enzyme activity, reduced liver blood flow and alterations in plasma drug binding may contribute to a decreased elimination of some metabolised drugs in the elderly. However, the authors concluded that it was difficult to separate an effect of ageing from a background of marked variation in the rate of metabolism due to factors such as individual metabolic phenotype, environmental influences, concomitant disease

states and drug intake. However, the current data suggest that initial doses of metabolised drugs should be reduced in the elderly population and then adjusted according to the clinical response (Durnas, Loi & Cusack 1990). Whether or not any of the above changes have an effect specifically on warfarin metabolism in the elderly is unknown, but all data are the result of early studies which would seem to suffer from several limitations, as discussed above.

In summary, the results of the above studies indicate that the debate on the effect of increasing age and an associated increased risk of bleeding in patients receiving warfarin therapy remains undetermined today. While it is generally accepted that particular care and close monitoring of the older patient receiving warfarin therapy is required, there has been no consistent evidence to support the theory that older age itself correlates with an increased risk for bleeding complications. Several studies have indicated that with modification of the management of older patients receiving warfarin therapy, bleeding complications can be significantly reduced and warfarin can be administered safely (Fihn et al. 1996; Jacobs 2003; Kagansky et al. 2004). The results of these studies further indicate the need for clarification as to whether age itself increases the risk of over-anticoagulation or whether older patients are more likely to bleed with a high INR than younger patients with a high INR. This will be further clarified in the current study by determining whether age is a significant factor in predicting an episode of over-anticoagulation and whether there could be an expected increase in the incidence rate ratio of episodes of over-anticoagulation while receiving warfarin therapy.

2.9 Effectiveness of anticoagulation among patients discharged from hospital

Because the risk of bleeding from warfarin is highest early in the first few months of treatment (Linkins, Choi & Douketis 2003), and patients discharged from hospital are at a high risk of experiencing adverse events (Forster et al. 2003), it is essential that the management of patients receiving warfarin therapy is of high quality, particularly during this early stage of therapy.

An aim of this study is to determine the INR control and warfarin management of patients from the first day of initiation in the hospital environment, through to discharge into the community. It is the intention of the researcher to determine the frequency of INR testing,

especially during the initial month of therapy, the rate of episodes of over-anticoagulation and the associated number of major bleeds that occur.

The results of recent studies in Australia and worldwide indicate that the usual practice of initiation of warfarin in teaching hospitals and subsequent discharge of patients to community care might result in poor outcomes (Jackson et al. 2004; Sowter, Feely & Kay 1997; The Newcastle Anticoagulation Study Group 1998).

An audit review of 100 consecutive patients starting warfarin therapy at Leeds General Hospital, UK, were identified to determine the quality of warfarin prescribed and whether any delay in patient discharge was due solely to failure to achieve optimal anticoagulation (Sowter, Feely & Kay 1997). Overall, the results of the study indicated that there was poor quality use of warfarin in the hospital with inappropriate dosing seen on several occasions and no consistent strategies for initiation of treatment. The appropriateness of the dosing was a value judgment made by the authors based on the baseline INR, the patient's age, weight, concurrent medical conditions and concurrent medications. An example of inappropriate dosing was determined when a 97-year-old woman received a 10 mg dose of warfarin on the first three consecutive days of treatment.

While INR testing was done frequently, that is, one test per 1.28 days of hospital stay, 37 patients had no pre-warfarin baseline INRs measured. There appeared to be little consideration given to age and weight, concurrent medications and sometimes concurrent diseases in those patients commencing therapy, and in several cases an undesirable effect of the INR occurred due to the omission of dose adjustments. The cause for delay in the discharge of 25 patients was solely attributed to difficulty in achieving the optimal anticoagulation level, which resulted in 68 extra days spent in hospital, while 16 patients were discharged without attaining a therapeutic INR level. Extrapolation of the discharge delays was estimated to be over 200 in-patient days per annum. Patients were not followed up on discharge from the hospital (Sowter, Feely & Kay 1997), resulting in their progress from there being unknown. It would appear from the data that although there was frequent testing of the INR, there was no consistent follow-up of those results. The study does not clarify whether doses were made based on a dosing nomogram or hospital protocol or the clinical judgment of the doctor prescribing the warfarin.

As a result of the study, new prescribing and monitoring documentation was introduced into all wards in the hospital to improve the management of warfarin and the pharmacist

became responsible for dosing and educating the patient until discharge, whereupon all necessary information was transferred to the out-patients clinic (Sowter, Feely & Kay 1997). The outcome of the introduction of these new procedures is not known.

A more recent, randomised controlled trial conducted by Jackson et al. (2004) in the Royal Hobart Hospital, a 450-bed acute care teaching hospital in Tasmania, found similar results in the period of initiation of warfarin therapy in the hospital setting, although this study followed the patients on discharge from the hospital. When examining the effect of a program that focused on the transition of newly anticoagulated patients from hospital to the community, there was found to be a significant decrease in bleeding complications during the first three months of treatment and an increased number of therapeutic INRs. Of the 128 patients involved in the study, 60 were randomised to a 'home monitoring' (HM) group and the remaining 68 to a 'usual care' (UC) group. The patients in the home monitoring group received a home visit by the project pharmacist and point-of-care INR testing on alternate days on four occasions, with the initial visit on the second day after discharge from the hospital. In addition, the pharmacist discussed educational aspects of the patient's warfarin treatment such as goals, possible adverse events and interacting medications and also delivered a standard educational booklet to the patient. Each patient was telephoned with his or her INR results and subsequent dose adjustments were made. The patients in the 'usual care' group were discharged home from hospital into the care of the GP only and received a visit eight days after discharge to determine anticoagulant control.

The median number of days that patients received warfarin prior to discharge was six in each group and there was no significant difference between the two groups with regard to anticoagulant control at discharge. Alarmingly, results showed that overall only 44% of patients had a therapeutic INR on discharge. However, there was a significant difference between the two groups of patients at day eight after discharge. It was found that 67% of patients in the HM group as opposed to 41% in the UC group were within the therapeutic range ($P<0.01$). Most importantly, 37% of patients in the UC group who were sub-therapeutic on discharge had a supra-therapeutic INR at day eight compared with nil in the HM group. Additionally, there was found to be a significant difference in total, major and minor bleeds between the two groups with 15 total bleeds in the HM group as opposed to 36 total bleeds in the UC group. Verification of the accuracy or comparison of the POC INR results with the laboratory INR results taken was not mentioned in the

study. If the POC INR results were recorded as being lower than the laboratory INR results, this may have skewed the overall results.

The findings of this study show that despite the accessibility of initiation protocols in the hospital, the introduction of warfarin therapy continues to present a problem. It also demonstrates that the introduction of a system's solution, that is, the home monitoring program, rather than concentrating on individual behaviour, improves overall outcomes. The aims of this program were to provide patients and their GPs with information regarding dose decisions at the point-of-care and an increased general knowledge and understanding of the drug, its benefits and adverse effects (Jackson et al. 2004). Kucukarslan et al. (2003) postulate that the failure to obtain sufficient information about the patient or about the pharmaceutical agent contributes to medication errors. In summary, the authors of this study postulated that it was highly likely that the combination of improved monitoring post-discharge and a patient-focused education program resulted in the reduction of the number of bleeding episodes post-discharge from the hospital (Jackson et al. 2004).

The results of a study conducted among patients discharged on warfarin therapy from the John Hunter Hospital, Newcastle, New South Wales, and their perspective GPs, support the theory that frequent monitoring of INRs facilitate the reduction of the incidence of bleeding complications and improve anticoagulant control. The authors of this study found that INR levels were safely controlled with a high frequency of laboratory testing performed, with complication rates comparable to those in previously published reports (The Newcastle Anticoagulation Study Group 1998).

In this study, the pathology department or GPs were contacted to obtain the details of the last ten measurements, within six months of discharge, of their patient's INR results, the total number of measurements within the six months of discharge and when they were carried out. The GPs were also sent a questionnaire to ascertain any complications of warfarin incurred during those six months following discharge and the INR level targeted. Patients were also sent a questionnaire consisting of ten questions that assessed their knowledge of warfarin and complications encountered during the same time. Completed questionnaires were received from 242 patients and the pathology records of 195 of these patients were examined (The Newcastle Anticoagulation Study Group 1998).

With regard to the frequency of INR testing, results found that they varied between less than one and eleven per month. The average time between INR values was seven days, but was greater than this in those patients with fewer tests. The maximum number of INR measurements within the six months of discharge was between 25-66, in which 39 (20%) of the patients fell. In this group, the median INR level over the six months was 2.7 compared with 2.3 in those patients with less than 10 INR measurements. Among the group of patients who had less than 25 INR measurements, those with an INR<2.0 were more likely to have their next measurement within one week than those with an INR value between 2.0-2.9, as were those with an INR level of 4.0 or higher. Most patients who had between 25-66 INR measurements during the six months had their next test within one week, irrespective of their previous INR level.

With regard to the target INR level aimed at, 37% of GPs aimed between 2.0-3.0, followed by 23% who aimed between 2.5-3.5. GPs aimed for the highest level of INR, 3.0-3.9, for those patients with artificial heart valves and appeared to aim for higher levels when patients had a pulmonary embolus as opposed to either a deep vein thrombus or AF. The INR levels were found to be below the target range on 29% of the days tested, within the target range on 54% of the days tested and above target range on 17% of days tested. Overall, the median INR level was found to be 2.4, with only 4% of observed patient time being spent at an INR of 4.0 or higher and 54% of observed patient time being spent at an INR level of 2.0-2.9.

Five patients experienced a major bleed during the six months of treatment, but 25% of all of the patients had been taking warfarin before their current hospital admission. The study did not clarify whether the five patients with a major bleed had been previously taking warfarin or not so it is not clear whether these five patients were taking warfarin for the first time and what may have been the cause of the bleed. For these five patients the median INRs fell between 2.0-3.0 at the time of their bleed. While the rate of a major bleed is slightly higher than reported in other studies (Atrial Fibrillation Investigators 1994; Palareti et al. 1996), this group of patients was a non-select group as opposed to the patients selected to enter other trials.

The results of the patient's questionnaires indicated that generally knowledge was poor. Only 3% of patients answered all questions correctly and 24% answered less than five questions correctly, but there was no association found between INR levels and knowledge of warfarin.

The findings of this study clearly indicate that anticoagulation control in the general practice rooms included in this study is of a good standard, with the majority of patients being controlled to targeted INR levels (The Newcastle Anticoagulation Study Group 1998). The frequency of INR testing in this study (The Newcastle Anticoagulation Study Group 1998) was much higher than in previously reported studies (Go et al. 2003; Gottlieb & Salem-Schatz 1994), possibly indicating that more frequent INR monitoring may allow for variations in INR values to be picked up earlier and thus lead to a decreased incidence of episodes of over-anticoagulation.

In summary, it would appear that the success of the delivery of safe warfarin therapy in the above studies was primarily due to frequent INR monitoring with appropriate dosage adjustments, a comprehensive education program for the patients and their GPs and a systems approach to the problem rather than an individual approach. Additionally, it would appear that the failure to deliver safe warfarin therapy was due primarily to inappropriate dosing, inconsistent strategies for the initiation of treatment and little to no consideration given to the patient's age, weight or concurrent co-morbidities and medications.

2.10 Association between frequency of monitoring and INR control

This section will provide a review of the most recent literature pertaining to the unresolved debate of the association between the frequency of monitoring warfarin and improved INR control. According to Crowther (2003), medication errors that are specific to oral anticoagulants usually occur due to inadequate monitoring, co-administration of interactive medications or an inadequate response to excessive INR values. Thus, two of the objectives of this study are, firstly, to establish the frequency of INR monitoring that currently occurs in the hospital setting and in GP rooms, especially during the initial month of treatment, and secondly, to establish the degree of INR control during that time. A study conducted by White et al. (2007) established that good INR control is essential to improving patient outcomes and that INR control in the first 30 days of treatment is predictive of subsequent INR control. The premise behind improving the accuracy of anticoagulant control is that by avoiding episodes of over-anticoagulation, the frequency of bleeding complications will be reduced. Thus, a further aim of this study is to attempt

to determine if a lack of INR monitoring is associated with an increased number of episodes of over-anticoagulation.

Ansell et al. (2001) suggest that the monitoring of the INR by experienced and professional personnel reduces the risk of excessive or inadequate anticoagulation with the associated risks of bleeding or thrombosis. In the hospital setting, the initiation or the supervision of warfarin is likely to be attended to regularly and the use of experienced staff is likely to reduce out-of-range INR values and their associated complications (Crowther 2003). However, despite the presence of professional personnel and consensus guidelines in place, research indicates that control of oral anticoagulant treatment in the hospital or anticoagulation clinic setting remains suboptimal, particularly during the first three months after the initiation of warfarin therapy (Jackson et al. 2004; Menendez-Jandula et al. 2005). Recent studies have reported improvement in INR control and subsequent clinical outcomes due to improvement in the frequency of INR testing (Bond & Raehl 2004; Ezekowitz et al. 1999; Hambidge 2002; Jackson et al. 2004; Menendez-Jandula et al. 2005).

Poor control of warfarin therapy may lead to increased morbidity and mortality, frequent doctor visits, longer and more frequent hospital stays, and resultant increased health and hospital costs (Vadher, Patterson & Leaning 1997). In 1995, Bond and Raehl (2004) explored the association between pharmacist-provided anticoagulation management in hospitalised Medicare patients and such major health care outcomes as death rate, length of stay, Medicare charges, bleeding complications and transfusions administered in 717,396 patients in 955 hospitals in the US. Results indicated that in hospitals without the close monitoring of pharmacist-provided warfarin management, all of the major health care outcomes were significantly increased in patients receiving warfarin therapy. That is, the death rate was 6.20% higher (2,786 more deaths), length of stay was 5.86% higher (316,589 more patient days), Medicare charges were 2.16% higher ($234,275,490 more in patient charges), bleeding complications were 8.09% higher (429 more patients had bleeding complications) and the transfusion rate for bleeding complications was 22.49% higher (8,991 more units of blood were used). These results are significant considering that the study population represented only 28.25% of hospitalised Medicare patients who should be receiving anticoagulation treatment. Although the authors recognised several limitations, the findings of this study appear be robust and generalisable because of the large sample size, the inclusion of a large number of hospitals in the study and there being

only one major variation in the care of the patients, that is, pharmacist-managed anticoagulation, all of which add to the study's robust results. Additionally, the study involved a specific patient population of hospitalised Medicare patients needing warfarin therapy.

The outcome of this study indicates that the frequent monitoring of the INR values contributed significantly to the improved outcomes. That is, it would appear that because of close monitoring of the INR by the pharmacists, out-of-range INRs were potentially picked up earlier with appropriate dose adjustments made and as a consequence, patients spent less time exposed to potential bleeding risks or complications with significant reduction in costs to the overall health care system.

Further to this inference, there was a very recent study conducted by White et al. (2007) which analysed combined data from the SPORTIF (Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation) III and V trials to determine the relationship between INR control and the rates of death, bleeding, stroke or systemic embolic events (SEE), and myocardial infarction (MI) among patients randomised to receive warfarin. The authors of this study found that patients with poor INR control suffered increased rates of all of the abovementioned diseases. The study, which included 3,587 patients, compiled three equal groups to include those patients with good INR control, those with moderate INR control and those with poor INR control, according to the percentage time with an INR between 2.0-3.0. Outcomes, according to INR control, resulted in the poor control group suffering the highest rates of annual mortality (4.20%) and major bleeding events (3.85%) compared with the good control group (1.69% and 1.58%). The poor control group also incurred higher rates of MI compared with the good control group (1.38% versus 0.62%, P=0.04) and higher rates of stroke or SEE (2.10% versus 1.07%, P=0.02). Furthermore, major bleeding rates were less frequent in the moderate and good INR control group (P<0.01) (White et al. 2007).

The outcome of the study by White et al. (2007) indicates that patients with poor INR control had overall more than 2% per patient-year higher absolute total mortality than those patients with good INR control. The study also examined whether INR control during the initial six months of treatment predicted subsequent INR control. The outcome indicated that the 6-month INR control was indicative of the INR control for the rest of the study (16.6±6.3 months). That is, those patients with poor INR control during the initial six months of treatment were likely to have poor INR control in the long term

(White et al. 2007). A study by Hylek et al. (1994) found similar outcomes in that INR control during the initial 30 days of treatment was predictive of subsequent INR control. Results from these studies indicate that good INR control, derived from diligent monitoring and appropriate dose adjustments, were likely to result in better patient outcomes.

According to Ansell et al. (2001), there is growing evidence that improved outcomes are achieved when anticoagulation is managed by POC measurement in the professional setting as well as at home. The primary reason for this improved care has been attributed to the unlimited access, convenience and opportunity for increased frequency of testing of the INR when deemed necessary. Furthermore, self-testing provides the potential for increased knowledge, awareness and participation on behalf of the patient that may lead to improved compliance and ultimately more positive outcomes (Ansell et al. 2001; Bereznicki et al. 2006).

A small (n=46) randomised, prospective cohort study conducted in California, by White et al. (1989), compared the efficacy and accuracy of patients measuring their own PT at home following discharge from hospital immediately after starting warfarin for the first time with patients who received specialised anticoagulation clinic care. Of the 46 patients enrolled in the study, 23 were randomised to the home-monitor group and 23 to the anticoagulation clinic care group. The patient's warfarin dosing was managed by their health-care providers and patients were followed for eight weeks. There were no significant differences between the groups regarding demographic and clinical characteristics; however, results indicated that anticoagulation control was significantly superior in the home-monitor group compared with the anticoagulation clinic group. That is, the median percentage time that patients in the home-monitoring group were in the therapeutic range was 93% as opposed to 75% for patients in the anticoagulation clinic group ($P<0.005$).

Additionally, the median percentage of time in the target range improved significantly in the home-monitored group during the second 4-week period of follow-up compared with the first 4-week period (100% compared with 90%, $P<0.05$) with no improvement seen in the anticoagulation clinic group for the same period of time (66% compared with 66%). While there were no patients who experienced a major bleeding complication in either group during the study (95% CI; 0-12%), compliance was better in the home-monitor group, that is, 83% compared with 74% in the anticoagulation clinic group.

The authors of this study suggested that because of the ease and convenience of monitoring that was attained in the home-monitoring group, it was likely that more frequent testing with appropriate dose adjustments led to improved control, which is consistent with the results of the study conducted by Bond & Raehl (2004). Poor compliance in the anticoagulation clinic group did not correlate with poor control, suggesting that it was likely that a lower frequency of PT testing may have contributed (White et al. 1989).

Although this study could be criticised for its relatively small sample size and other limitations acknowledged by the authors (White et al. 1989), the results indicate that home monitoring provides accurate measurements and, most importantly, that appropriate dose adjustments can be achieved with more frequent INR monitoring.

A larger study (n=260) that examined data taken from patients randomised to anticoagulation therapy in the SPINAF study, a multi-centre clinical trial conducted between 1987-1991 in Portland, Oregon, found that frequent INR testing would appear to improve outcomes (Ezekowitz et al. 1999). These results supported the findings of the study by White et al. (1989). This study examined, in particular, the need for frequent monitoring in patients receiving warfarin therapy. Results indicated that during the induction period of the first 12 weeks, the proportion of patients whose PTRs were in the desired target range increased from 28% at one week post-randomisation to 65% at 12 weeks post-randomisation with a weekly PTR testing regime. Thereafter, the testing was reduced to monthly for the maintenance period of a further 156 weeks. The percentage of patients with stable doses during the maintenance period fluctuated between 10-25%, indicating that more frequent monitoring was needed. The most significant finding of the study overall in the authors' view was that outpatient warfarin therapy could easily be initiated at the anticipated maintenance dose, but that careful monitoring was required (Ezekowitz et al. 1999).

A recent randomised controlled trial conducted by Menendez-Jandula et al. (2005), in a university-affiliated hospital in Spain, comparing the quality of control and the clinical outcomes of oral anticoagulant therapy in self-managed patients versus patients following conventional management, found very similar outcomes to the study by White et al. (1989) and Ezekowitz et al. (1999). A total of 737 patients were randomly assigned to one or the other group and all were treated with acenocoumarol. The median follow-up period extended to 11.8 months. Results indicated that while the quality of INR control was

essentially similar in the self-management group and the specialised management group, the self-management group was superior in terms of reduction of total major complications, that is, 7.3% versus 2.2%. Minor bleeding complications were recorded as 36.4% in the specialised management group as opposed to 14.9% in the self-management group. Most importantly, it was estimated that the patients in the self-management group had a 70% reduction in the risk for severe haemorrhage and thromboembolic disease (Menendez-Jandula et al. 2005).

The patients in the self-management group were able to perform an INR test whenever they felt it was required, whereas the patients in the conventional group received an INR test once every four weeks. The most notable findings of this study were that patient self-management of oral anticoagulant therapy decreased the incidence of major bleeding complications and improved clinical outcomes with comparable quality of anticoagulation management (Menendez-Jandula et al. 2005). These results provide further evidence that the principles of self-management, that is, frequent INR monitoring and improved patient education and compliance, leads to a better quality of anticoagulation and reduced risks.

While the outcomes of self-management appear to be considerably improved, when compared to the outcomes of high-quality anticoagulation management delivered by an anticoagulation clinic, the differences between the two methods of management are less marked (Hirsh et al. 2003). Results from recent studies comparing the two management strategies further suggest that patient self-testing or patient self-management offers limited advantages. Both Gadisseur et al. (2003) and Kaatz, Elston-Lafata and Gooldy (2001) found that the time patients were in the therapeutic range was similar regardless of whether patients self-tested and self-managed or were managed by an anticoagulation clinic. Cromhecke et al. (2000), in a randomised crossover study involving 50 patients managed either by an anticoagulation clinic or by self-management, found that although there was a trend towards greater time in therapeutic range in the self-management group (55% versus 49%), it was not a significant difference.

It would appear from the findings of these studies that three areas of management contributed significantly to improved outcomes: the high quality of management administered, the increased frequency of INR monitoring and improved patient education and subsequent compliance.

In a record linkage study by Jones et al. (2005), conducted in Cardiff and South Wales, UK, and involving 2,223 patients with nonvalvular AF and receiving warfarin therapy, it was found that patients were least likely to die or be admitted to hospital when their INR values were nearer to the mid point of the target range. The authors showed that instability of the INR had significant implications for mortality and other clinical outcomes and that there was an association between INR values outside the target range and increased rates of hospitalisation. Additionally, it was shown that a 10% increase in the time spent outside of the target range was associated with an increase in the likelihood of death of 29.3%. Patients were found to be above the target range, that is, above 3.0, 15.4% of the time and the median time between INR tests was 16 days. Most notably, the study found that INR control was at its worst in the first three months of therapy and was subsequently associated with an increased risk of adverse events (Jones et al. 2005). There were no recorded details as to the frequency of INR monitoring during the first month of treatment.

While it would be simplistic to assume a direct relationship between the frequency of INR monitoring and INR control, it would seem realistic and reasonable that more frequent monitoring would elicit INR values that were outside the target range and allow for appropriate dose adjustments to be made, especially during the unstable first three months of therapy. Yet simply increasing the frequency of INR monitoring would not appear to solve all of the problems. While the primary goal of warfarin therapy is to deliver the lowest possible dose that prevents propagation or recurrence of clot formation, it is equally important that patient safety is maintained. In attaining this goal, finding a monitoring schedule that balances patient safety with patient discomfort, cost and the inconvenience of monitoring must be found (Glasheen 2005). Furthermore, Glasheen (2005) postulates that to achieve this outcome, it is necessary for the clinician to recognise that the frequency of INR monitoring must be flexible and adaptable according to the patient's risk of over-anticoagulation.

In summary, it would appear that the significance of these studies lies in the frequency of INR testing with appropriate dose adjustments and improved patient education including an awareness of adverse effects resulting in subsequent improved compliance. In Australia, INR testing may be attended to approximately once every 4-6 weeks in those patients who have a very stable INR, no interacting medications and low bleeding risk according to the consensus guidelines (Gallus et al. 2000; Hirsh et al. 1998), while the

frequency of INR testing may be extended to up to 12 weeks in Britain according to the third edition of the guidelines on oral anticoagulation, the most recent ones, developed by the British Society for Haematology (Baglin & Rose 1998). Conversely, patients with access to POC monitoring are able to check their INRs whenever they deem it necessary. The benefit of this would appear to be that clinic or GP managed patients have a longer period of time for their INRs to vary from the target range before being picked up and this is reflected in the greater percentage of both major and minor bleeding complications and thromboembolic events found in the study by Menendez-Jandula et al. (2005) and out of range INR values seen in the study by Jones et al. (2005). Additionally, adjustments may be made without rechecking the INR for at least one to two weeks or longer with unknown outcomes. Home management patients are able to pick up variations in INR values more frequently and conveniently, monitor those results and receive an adjustment to their warfarin therapy if necessary.

In conclusion, high-quality management of this therapy will become increasingly important with the expansion of clinical indications for the use of warfarin in thromboembolic disease states. Responding to this challenge will require improvements not only in the biomedical treatment, but also in the delivery of care (Beyth 2005). The above studies provide further evidence that patient self-management, or the result of self-management, that is, more frequent INR monitoring and more compliant patients, may significantly contribute to a greater number of patients being within their target INR range and thus experience more successful and safer warfarin therapy. Yet, as previously mentioned, the frequency of INR monitoring must be balanced with patient safety, convenience to the patient and cost incurred. This study will explore the frequency of current INR monitoring in association with the number of episodes of over-anticoagulation.

2.11 Managing warfarin therapy

The initiation of consensus guidelines in recent times has provided strategies for clinicians to deliver high-quality management to minimise the risk of bleeding. These recommended guidelines are taken from the proceedings of the Fifth American College of Chest Physicians Consensus Conference on Antithrombotic Therapy (Hirsh et al. 1998) and are consistent with the most recent 'Guidelines on oral anticoagulation', developed

by the British Society for Haematology (Baglin & Rose 1998), the 'Consensus guidelines for warfarin therapy' as recommended by the Australasian Society of Thrombosis and Haemostasis (Gallus et al. 2000), and the consensus guidelines 'Warfarin reversal', developed on behalf of the Australasian Society of Thrombosis and Haemostasis (Baker et al. 2004).

This section will review and discuss the strategies and guidelines identified in minimising bleeding risks prior to and at the commencement of warfarin therapy and during the course of therapy. Thus, an objective of this study is to assess the current medical trends and concepts of medical management in patients receiving warfarin therapy.

2.11.1 Initiation of warfarin therapy

As discussed above, the most common adverse effect of warfarin therapy is bleeding complications (Campbell et al. 2001). Thus, when considering a patient for warfarin therapy, it is crucial to recognise the patient's risk of bleeding and to make an accurate assessment of the risk:benefit ratio for that individual. Scoring systems have been proposed to help stratify the patient's risk for a bleed (Beyth, Quinn & Landefeld 1998; Campbell et al. 2001) by simply identifying a patient's history. Those factors that have been identified as markedly increasing a patient's risk to incur a bleed are as follows: age>65-70 years, a high target INR, the presence of cerebrovascular disease, a history of gastrointestinal bleed or ulceration, liver disease, other co-morbid conditions such as congestive cardiac failure, anaemia, hypertension, active malignant diseases or diabetes, personal or family history of bleeding disorders and a history of falls (Baker et al. 2004; Campbell et al. 2001; Ho & Brighton 2002; Levine et al. 2001). Those factors that are considered to moderately increase the risk of a bleed are as follows: age between 60-70 years, chronic renal failure, the presence of interacting medications, a change in poor nutrition, large fluctuations in the INR level and the first three months of warfarin treatment (Campbell et al. 2001). Along with the patient's history, a baseline blood test to include INR, haemoglobin level, activated partial thromboplastin time (aPTT) albumin, platelet count and liver function tests should be carried out to complete the individual patient's picture (Baglin & Rose 1998).

Setting an appropriate target INR that balances the therapeutic goal with the risk of bleeding on an individual basis is a key element to optimising warfarin therapy that will

reduce bleeding risks and maximise antithrombotic effects (Baker et al. 2004). While the target INR varies for different clinical situations (Gallus et al. 2000), the usual target INR for most conditions is 2.0-3.0 (Campbell et al. 2001). Reducing the target INR to less than 2.0 has not been proven to be as effective to reduce bleeding risks (Hylek et al. 2003). Although a common practice, loading doses do not appear to offer an advantage in reaching a therapeutic INR level sooner (Gage, Fihn & White 2000). Because high loading doses of warfarin may result in bleeding episodes, it is preferable to commence patients on an initial daily dose of 5 mg, or a dose that is close to the usual maintenance dose of approximately 4-6 mg per day (Campbell et al. 2001; Hirsh et al. 1995; Hirsh et al. 2003). Dosing nomograms are also a common method by which to commence patients on warfarin. The most commonly used nomogram is that devised by Fennerty et al. (1984) or those modified from the Fennerty nomogram (Campbell et al. 2001).

When patients are commenced on warfarin, it is recommended that the duration of therapy is determined in advance and tailored to the individual with periodic re-evaluation of the patient's harm:benefit ratio throughout the therapy (Ho & Brighton 2002).

It has been suggested by Campbell et al. (2001) that patients considered to be at an immediate risk of further embolic complications, such as patients with deep venous thrombosis, pulmonary embolism or embolic stroke, should be commenced on heparin or low molecular weight heparin in conjunction with warfarin for a period of 4-5 days until the INR has been in the therapeutic range for 48 hours. Those patients considered to be at less risk, such as patients with stable AF without embolic events, require warfarin only (Campbell et al. 2001).

It is recommended that patient education and compliance is encouraged from the initiation of treatment. It has been reported that those patients who have a poor understanding of warfarin and its adverse effects are more likely to be non-compliant than those who have an understanding of the drug and receive effective education (Arnsten, Gelfand & Singer 1997). It is further recommended that patients report any signs of bleeding, suggest increased frequency of INR testing when starting or stopping other medications, either prescribed or complementary, keep a written record of INR results and warfarin dosages, and only maintain the one brand of warfarin throughout the treatment period (Campbell et al. 2001). In a response to a question put forward by F.K. Fry (General Practitioner) regarding the bioequivalence of coumadin and marevan, The Boots Company (1997), manufacturers of both brands of warfarin in Australia, stated that

> the bioequivalence of coumadin and marevan has never been tested, rather than they are not bioequivalent. It is on the basis that there are no data to confirm bioequivalence that they have been deemed not to be interchangeable, since it is conceivable that differences in bioavailability might seriously affect the level of anticoagulation. (1997:33)

Furthermore, because the strengths of coumadin tablets are 1 mg, 2 mg and 5 mg and marevan tablets are 1 mg, 3 mg and 5 mg, it has been suggested that patient compliance may be compromised due to confusion of the strengths of the tablets (Barnett 1991). Additional lifestyle factors, such as consistency of dietary intake of vitamin K, minimising alcohol intake, avoidance of binge drinking and reducing activities that may incur considerable risk of injury should be discussed with the patient being initiated on warfarin therapy (Ho & Brighton 2002).

2.11.2 Maintenance of warfarin therapy

According to Ho and Brighton (2002), once warfarin therapy has been initiated, conscientious management of the INR is the key to minimising bleeding complications and maintaining successful treatment, with a blood test every 1-2 weeks being required in some cases throughout the duration of therapy. The authors believe that 'instability of the INR can be predicted' (Ho & Brighton 2002:85). Because the INR is a good indicator of the effectiveness of treatment and the risk of bleeding during warfarin therapy (Gallus et al. 2000), the doctor should be prompted to initiate more frequent INR testing if there is a change in the following: a patient's health, lifestyle or medications or when dose adjustments are made (Gallus et al. 2000; Ho & Brighton 2002). While dose adjustments should be made on every occasion that the INR value is outside the preset target range, and there should be only a narrow tolerance of veering from the target range of INR (Ho & Brighton 2002), frequent dose adjustments should be avoided (Baker et al. 2004). An INR tested approximately one week after a change in medication will reflect a clinically significant interaction (Baker et al. 2004). Because a change in warfarin dose takes several days to influence the INR, testing the INR within 24-28 hours of a dose change will not provide a true steady-state response to the dose adjustment. Additionally, avoidance of excessive increases in dosage when the INR value drops below the target INR range is also prudent (Baker et al. 2004).

It is recommended that any time the INR value is found to be outside the target range, the physician look for a cause. The cause of the aberrant INR may not be associated with the patient but may be due to a laboratory error, but nevertheless, it is recommended that it be investigated (Gage, Fihn & White 2000).

The initial frequent INR testing can be reduced to once per week or once per fortnight if the INR is stable, and those patients who have a very stable INR, are taking no interacting medications and are at a low risk of incurring a bleed may require a test only once every 4-6 weeks (Campbell et al. 2001). Although this is the recommended regime at present, according to Ansell et al. (2001), there is growing evidence to suggest that more frequent testing of the INR will lead to more time in the therapeutic range. Because the highest risk of bleeding is during the initial three months of therapy, careful monitoring is warranted during that time (Ezekowitz, et al. 1999).

2.11.3 Management of episodes of over-anticoagulation

This section will not detail all aspects of the individual treatment of over-anticoagulation, but will focus on the general principles that are recommended in the approach to the management of episodes of over-anticoagulation or unstable dose responses.

It is widely acknowledged that there is a close relationship between the level of INR and the risk of bleeding, that is, the risk of bleeding increases markedly once the INR exceeds 4.0 and increases sharply with a value greater than 5.0 (Baker et al. 2004). Because the effectiveness and the safety of warfarin therapy is dependent on maintaining the INR within the therapeutic range, any episodes of over-anticoagulation or an unstable dose response should trigger a review of the need for warfarin and continued therapy must be closely followed both to detect the cause of the bleed, if present, and to avoid further over-anticoagulation (Gallus et al. 2000). Thus, the initial step in the management of over-anticoagulation is to attempt to identify and correct the cause (Campbell et al. 2001). Because many causes of over-anticoagulation are preventable, the investigation should be individualised, with particular attention paid to the level of the INR, the risk of bleeding and if bleeding is present, the clinical significance of the bleed (Baker et al. 2004). Common causes such as the presence of an interacting medication, deteriorating liver function, patient error or concurrent illnesses should be considered. In addition, the

reason for warfarin therapy and whether it is safe to continue with the therapy should also be considered (Campbell et al. 2001).

According to Hirsh et al. (2003), the absolute daily risk of bleeding is low even when the INR is excessively prolonged, leading many clinicians to manage patients with INR levels as high as 5-10 by stopping warfarin only, unless the patient is at a high risk of bleeding or already bleeding (Hirsh et al. 2003). After warfarin has been stopped, the INR falls over several days, that is, an INR between 2.0-3.0 will return to within a normal range in 4-5 days (White et al. 1995), as opposed to a substantial drop in the INR within 24 hours after the administration of vitamin K_1 (Crowther 2000).

In Australia, the guidelines for the management of over-anticoagulation are well established in recently published recommendations by The Australasian Society of Thrombosis and Haemostasis (Gallus et al. 2000). Additionally, the American College of Chest Physicians published recommendations for managing patients with coumarin anticoagulants who need their INRs lowered because of either actual or potential bleeding (Ansell et al. 2001). However, findings from a study by Bajorek et al. (2007) conducted in Sydney, NSW, to identify the views of health professionals, patients and their carers on the management of warfarin in older patients with AF, suggested that more information for hospital-based doctors and GPs was needed to support the decision to initiate warfarin therapy and to disseminate clinical trial data in order to provide a rationale. The study also suggested that although doctors were aware of the published guidelines available, many doctors, especially GPs wanted practical and interactive advice, rather than position statements, for dealing with acute situations such as episodes of over-anticoagulation and bleeding along with more interaction with specialists (Bajorek et al. 2007).

The choice of approach to the treatment of over-anticoagulation is at present based largely on clinical judgment because no randomised trials have compared the strategies of treatment with clinical end points (Hirsh et al. 2003). In summary, it is recommended that the overall management of episodes of over-anticoagulation be dependent on the risk of bleeding, the clinical significance of the bleed and the level of the INR (Baker et al. 2004).

2.12 Patient education: relationship between patient knowledge and anticoagulation control

It has been suggested that good patient compliance is necessary to safely realise the full benefits of anticoagulation (Arnsten, Gelfand & Singer 1997). Even though the effectiveness of warfarin has been proven and the number of patients receiving the anticoagulant has dramatically increased in recent times (Sudlow et al. 1995), a frequent explanation for physicians' reluctance to initiate patients on warfarin therapy has been poor patient compliance, especially among the elderly population (Kutner, Nixon & Silverstone 1991).

In this section, the issue of patient knowledge, anticoagulant control and determinants of compliance will be addressed. In this study, the reasoning behind questioning patients soon after the occurrence of an episode of over-anticoagulation is to ascertain their degree of compliance with the therapy leading up to the episode and their understanding of potential adverse effects of warfarin therapy. Therefore, one of the aims of this study, in determining whether episodes of over-anticoagulation are potentially preventable, is to establish the patient's degree of compliance, the level of warfarin knowledge and the health status of patients shortly before such an episode.

Studies conducted in Australia and overseas in evaluating the determinants of patient compliance and knowledge, have reported that patients' knowledge while receiving warfarin therapy is generally poor (McCormack et al. 1997; Tang et al. 2003; The Newcastle Anticoagulation Study Group 1998). Moreover, adequate adherence to warfarin therapy has been reported to be low, resulting in a significant effect on good INR control (Kimmel et al. 2007).

A recent study by Tang et al. (2003) found that the patient's knowledge of warfarin therapy had an important impact on anticoagulation control. Tang et al. (2003) conducted a prospective study of Chinese patients attending a warfarin clinic at the Prince of Wales Hospital in Hong Kong to evaluate their knowledge of warfarin therapy and adherence to medical advice and its relationship to anticoagulation control. The number of INRs that were within the target range in the last four visits to the clinic was also noted. The results of the study showed a positive correlation between patient's knowledge and the number of INR values that were in the therapeutic range ($r = 0.20$; $P = 0.024$). Additionally, the number of patients having INR values within the target range declined with increasing

age ($r = -0.30$; $P<0.01$). Of the 122 patients who completed the nine questions, the overall score, out of a possible maximum score of 1.0, was 0.48±0.18, indicating poor knowledge among participants. Only 40-45% of participants knew the strength of their warfarin tablets, the reason for taking warfarin and its effect on the body. Even more obvious was their lack of knowledge with respect to possible consequences of under- or over-anticoagulation, drugs that may interact with warfarin and what to do if a dose was missed. While previous studies conducted to assess the determinants of patients' knowledge also found poor knowledge (McCormack et al. 1997; The Newcastle Anticoagulation Study Group 1998), Tang et al. (2003) found that there was an inverse relationship between age and the knowledge score of the patient ($r = -0.43$; $P<0.001$). Previous studies had found that patients with increasing age were more likely to be compliant (Arnsten, Gelfand & Singer 1997; Monane et al. 1994), which is in contrast to the findings of Tang et al. (2003). Furthermore, Tang et al. (2003) found that longer duration of therapy and the acquisition of information from booklets were associated with better knowledge. Overall, it was found that after patient education became a part of the structured management program, patient knowledge and drug compliance, anticoagulant control and outcomes all tended to improve (Tang et al. 2003). While the study by Tang et al. (2003) would appear robust in its methodology, the questionnaires failed to address the issue of dietary factors or compliance resulting in patients' knowledge accounting for only 4% of the variance in anticoagulation control. Moreover, concurrent events in the underlying medical condition of the patient or use of interactive drugs were not considered, which may have further reduced the variance found.

Previously, a case-control study conducted in a Massachusetts hospital by Arnsten, Gelfand and Singer (1997) had attempted to assess the determinants of compliance with anticoagulant therapy among 43 patients discharged from the Anticoagulant Therapy Unit for noncompliance and 89 randomly selected patients who were reportedly compliant. Interviews conducted via telephone assessed patients for sociodemographic features, indication for warfarin, patient satisfaction and health beliefs. Results indicated that non-compliant patients shared distinctive clinical characteristics. They were more likely to be younger, male and non-white and less likely to have experienced a thromboembolic event. Interestingly, patients younger than 53 years were found to be many times more non-compliant than those in the oldest quintile of greater than 78 years, which was consistent with the findings of a study conducted by Monane et al. (1994) who found

compliance was best in women and white patients in a group of patients over 85 years and suffering from congestive heart failure.

Furthermore, non-compliant patients were more likely not to have a regular physician, and overall felt more burdened by taking warfarin and perceived fewer health benefits when receiving warfarin therapy. These patients were found to be more likely to either forego INR monitoring because of a perceived lack of benefits or cease warfarin therapy completely (Arnsten, Gelfand & Singer 1997).

Most strikingly, older patients were found to be more compliant with both warfarin dosing and INR monitoring, which was in conflict with the results of the study by Tang et al. (2003), but as their study was conducted in a Chinese population, it appears rational to consider that a cultural difference in the older population may have existed and impacted on the results of the study. Overall, the study by Arnsten, Gelfand and Singer (1997) found that important features associated with good compliance of patients taking warfarin therapy included good patient education, physician involvement and convenience associated with INR monitoring. Moreover, these authors suggested that the convenience associated with home monitoring might reduce the burden of frequent monitoring and lead to more optimal anticoagulant control as has been demonstrated in several studies conducted prior to and following the present study (Ansell et al. 2001; Menendez-Jandula et al. 2005; White et al. 1989). Arnsten, Gelfand and Singer (1997) did not determine the impact of compliance or education in association with anticoagulation control.

A recent report by Campbell et al. (2001) supports the previous findings of Arnsten, Gelfand and Singer (1997) and Beyth, Quinn and Landefeld (2000), by reiterating that patients who have a poor understanding of the indications and potential adverse effects of warfarin are more likely to be non-compliant. It has been suggested that patients should be encouraged to actively participate by reporting signs of bleeding while on warfarin, maintain a written report of INR results and dosages and detail newly introduced or deleted medications to their physicians for more frequent monitoring, and remain on one or the other brand of warfarin currently available. Additionally, it is recommended that prior to discharge from hospital education booklets be made available to patients (Campbell et al. 2001).

The combination of the trend to early discharge of patients after initiation of warfarin therapy and the complexities of the therapy itself makes it essential that the transfer of

information to patients and successively their GPs is vital (Jackson et al. 2004). A descriptive study conducted by Cheah and Martens (2003) in Columbus, US, involving 50 patients, sought to determine the level of knowledge of patients receiving warfarin therapy one week after discharge from an acute care hospital. Results indicated that patients exhibited an overall knowledge deficit about warfarin. As a result of the study, the authors suggested that emphasis should be placed on the following six areas of patient education: the patient must be taught about the action of warfarin and in terminology that is understood by them; the patient should be instructed about potential bleeding and signs to watch out for, and should be instructed about the potential for medications to interact with warfarin. Further instructions should be given about the importance of maintaining a consistent dietary intake, and the instructions should be tailored to the learning needs of the elderly (Cheah & Martens 2003).

Conversely, a cross-sectional survey of 52 patients attending two anticoagulation clinics in the Bronx, New York City, conducted by Davis et al. (2005) to assess the association between the impact of adherence, knowledge and quality of life with anticoagulation control, found that although adherence was significantly associated with anticoagulation control, patient demographics, knowledge about warfarin therapy and perceived impact of warfarin on the quality of life were not. Results of the study indicated that while only 14% of the patients experienced good anticoagulation control, 50% of the patients were reported as having adequate adherence to their therapy and 37% had good knowledge of anticoagulant control. Adequate adherence was significantly associated with good anticoagulation control (P=0.01). The findings that 73% of participants who reported adequate adherence to their therapy had poor anticoagulation control may suggest that either participants did not report accurately or that other factors, such as drug interactions or diet associated factors, genetic variability or frequent dose adjustments, which were not measured in the study, contributed to poor control. The method of data collection used involved an assessment of self-reported adherence, thus allowing patients to subjectively answer the questionnaire. These results may have been attributable to unrecognised confounding bias as patients may have perceived a higher level of adherence than was actually attained. Despite the findings of poor knowledge and good anticoagulant control among patients, most participants did not perceive warfarin to have a negative impact on their quality of life (Davis et al. 2005).

A prospective cohort study conducted in three anticoagulation clinics in Pennsylvania by Kimmel et al. (2007) attempted to quantitatively evaluate the effects of inadequate adherence to warfarin therapy on anticoagulation control. The Medication Event Monitoring System (MEMS) medication bottle cap (by Aardex), which records the exact time and date the pill bottle is opened, was attached directly onto each patient's warfarin bottles or alternative containers. Questionnaires were also given to patients to obtain information regarding changes in medications, changes in vitamin K intake or alcohol consumption, weight change and instructions by practitioners to temporarily stop taking their warfarin. Of the 136 patients observed for a mean of 32 weeks, 92% had one missed or extra bottle opening, 36% of patients had missed more than 20% of their bottle openings and 4% had more than 10% extra bottle openings. Multivariable analyses indicated that under-adherence was significantly associated with under-anticoagulation ($P<0.001$) in all categories in which patients missed more than 20% of bottle openings. The association between under-adherence and INR results below 1.5 was even stronger. Subsequently, over-adherence was significantly associated with over-anticoagulation in patients who had extra bottle openings on more than 10% of days (Kimmel et al. 2007).

Although the patients in the study by Kimmel et al. (2007) were constantly reminded of the importance of adherence to their warfarin therapy, results demonstrated poor adherence to their warfarin therapy in both the initiation and maintenance phases, with 40% of patients experiencing clinically significant levels of poor adherence, potentially creating a major source of poor anticoagulation control in the community. The outcomes of even small reductions in the INR below the therapeutic range is known to be associated with substantial risks for thromboembolism (Hylek et al. 1996), not to mention the need for increased dose changes, additional visits to the doctor and further potential for dosing errors (Kimmel et al. 2007). Although the authors of the study acknowledged the presence of several limitations to their study, the results clearly demonstrated that the lack of adherence to warfarin therapy by patients affects anticoagulation control and that even moderate levels of non-adherence are clinically important.

The study by Beyth, Quinn and Landefeld (2000) was a randomised controlled trial ($n=325$) that appeared to be robust and free of confounding or selection bias. The findings of this study were significant in that it was estimated that a comprehensive management program involving guideline-based stratification of risk factors and patient education, coaching and self-monitoring of INR values may reduce the rate of major bleeding by

half or more over the first six months of treatment (Beyth, Quinn & Landefeld 2000). The study was conducted at University hospitals in Cleveland, Ohio, and included patients 65 years and older who were stratified according to baseline risks for a major bleed using the Outpatient Bleeding Risk Index (Beyth, Quinn & Landefeld 1998) and randomly assigned to either an interventional group (n=163) or a usual care group (n=162). The patients in the intervention group received one-on-one teaching, using a specifically formatted workbook aimed at increasing patients' participation in their care and improving their information-seeking skills. Lastly, patients were taught self-monitoring of their prothrombin time by use of a POC machine. The patients in the usual care group received medical care according to the discretion and practices of their personal physician (Beyth, Quinn & Landefeld 2000).

Outcomes of the study not only revealed a reduction in the frequency of major bleeding in the intervention group, but comprehensive and significantly improved INR control. That is, the patients in the intervention group were found to be in the therapeutic range more than half the time during the first month of treatment as opposed to the usual care group whose INRs were found to be sub-therapeutic more than one third of the time during the same period of time. The usual care group went on to experience sub-therapeutic INR results most of the time thereafter (Beyth, Quinn & Landefeld 2000).

In summary, when one considers all the factors that may alter the dose-response relationship of warfarin and therapeutic INR values, there would appear to be a need to identify patients' knowledge strengths and deficits regarding their warfarin therapy in order to safely manage the drug. While a patient's knowledge and subsequent compliance is only one determinant of the dose-response relationship, it could be argued that it is a very important one. It would appear from the studies reviewed that our knowledge of the association between patient compliance, education and anticoagulation control remains incomplete. Thus, an objective of this study is to ascertain a patient's level of knowledge of warfarin and its side effects and the patient's general health status in the week leading up to an episode of over-anticoagulation.

2.13 Conclusion

In summary, this chapter has provided a critical analysis of the literature relevant to the research problem and identified the aims and the objectives of the study. Initially, the

literature investigation provided an introduction to warfarin and a brief background to its history and use. Following on from this, the first five sections briefly identified the complexities of the pharmacokinetics and dynamics of warfarin in the body, the indications for its use and the anticoagulant effect as opposed to the antithrombotic effect of warfarin. The study identified that warfarin is still today the mainstay of treatment for long-term anticoagulant therapy, and although there have been several studies investigating alternative oral anticoagulants, such as ximalagatran, warfarin remains the only widely available oral anticoagulant agent at the present time. According to Garcia et al. (2005), it is likely that it will remain as such for the foreseeable future. While the effectiveness of warfarin has been well proven, the maintenance and control of the INR within the optimal target range remains a difficult and complex task.

The major section of this chapter focused on the main side effect of warfarin, haemorrhagic complications. Identification and discussion of those clinical variables associated with increasing the risk of bleeding complications followed. They were identified as drug and food interactions, genetic factors and age. The effectiveness of anticoagulation in patients discharged from hospital was also discussed. When one considers all of the factors that may alter the dose-response relationship of warfarin, it is understandable how difficult it is for physicians to maintain optimal INR control.

The next section of this chapter discussed the three main areas of management that would appear to contribute significantly to optimal INR control. The topics discussed included the association between the frequency of INR monitoring and INR control, the concepts of physician management and elucidation of the consensus guidelines in the management of patients, and the relationship between patient knowledge and anticoagulant control. These three concepts of management are the key issues to be investigated in this study. Thus, the objectives of this study are to determine the frequency of INR monitoring that currently occurs in both the hospital setting and in the GPs' rooms and the number of episodes of over-anticoagulation during the initial five months of warfarin therapy, specifically the number in the first month compared with subsequent months. Further objectives are to assess the health status, the level of warfarin knowledge and the degree of compliance of patients immediately prior to an episode of over-anticoagulation, and to determine current medical trends and assess the concepts of medical management of patients. Finally, the research question will be addressed, that is, are the number of episodes of over-anticoagulation potentially preventable or unforeseeable?

It would appear from the literature that warfarin is here to stay for the near future at least. With the number of patients receiving warfarin therapy dramatically increasing in Australia and overseas, particularly in the elderly population, it is essential that exposure to potential risks and complications by patients is minimised. It is the aim of this study to investigate the present process of management of patients being initiated on warfarin therapy for the first five months of therapy by collecting data about the phenomenon in order to meet the objectives of the study and draw conclusions that go towards answering the research question.