Chapter Five

Discussion and Conclusions

5.1 Introduction

This thesis has examined the process of management of patients receiving warfarin therapy through the hospital/community interface from initiation for a period of five months, or less if warfarin therapy was ceased prior to this time. In order to research this process an exploratory, descriptive survey was utilised as it provided the researcher with the required objective data in a way that was least invasive to the participants in the study. Furthermore, it provided a 'snapshot' concerning the complex phenomenon under study and captured the full and true nature of the process of management as it occurred naturally in clinical practice.

Warfarin has proven to be a very effective oral anticoagulant for the primary and secondary prevention of thromboembolic events, which has given rise to a substantial increase in its usage throughout the world including Australian hospitals. Yet, while worldwide usage of warfarin has increased, some practitioners still remain reluctant to initiate patients on warfarin therapy due to its adverse side effects. The maintenance and control of the INR within the optimal target range and the prevention and management of episodes of over-anticoagulation remains a difficult and complex task. Several studies have shown that excessive anticoagulation with a prolonged INR above 4.0 increases the risk of bleeding complications exponentially. While efforts are being made to introduce new oral anticoagulants, it would appear that now and in the foreseeable future warfarin remains the only widely available oral anticoagulant agent.

This thesis has reviewed and critically examined the literature pertaining to these issues, in particular, the prevention of episodes of over-anticoagulation associated with warfarin therapy in patients with thromboembolic disease. On the basis of the overall literature review, it was concluded that factors that may contribute to the occurrence of episodes of over-anticoagulation include patient-related factors such as compliance and education, the presence of co-morbid conditions, older age (>75 years) and early management strategies such as the frequency of INR monitoring and therapeutic activity that deviates from current best practice.

It has been argued that patients are at the greatest risk of bleeding in the first few months of treatment and that INR control in the first six months of treatment is predictive of subsequent INR control. Furthermore, several studies have predicted that patients being discharged home from hospital may be at a high risk of incurring an adverse event.

Thus, there were five objectives of this thesis. The first objective was to determine the frequency of INR monitoring that currently occurred in both the hospital setting and in GP rooms, especially during the initial month of treatment. The second objective was to determine the number of episodes of over-anticoagulation during the initial five months of treatment, especially the number during the initial month compared with subsequent months. The third objective was to determine the number of major bleeds that occurred during the first five months of treatment, both those associated and those not associated with an episode of over-anticoagulation. The fourth objective was to assess the health status, the level of warfarin knowledge and the degree of compliance of patients prior to an episode of anticoagulation, and the fifth and final objective was to establish the current medical trends used in the management of patients receiving warfarin therapy.

Finally, the five objectives of this study led the researcher to formulate the research question 'Are episodes of over-anticoagulation potentially preventable or unforeseeable?' In order to address the research question, the findings with regard to the first five objectives were taken into consideration along with the inferential analyses of those covariates thought to be significant predictive factors of an episode of over-anticoagulation. Those covariates included the effect of age, gender, frequency of monitoring during the initial month of treatment, serum albumin, Hb, the Hospital at Home Services, antibiotics, CCF, amiodarone, paracetamol, decreased oral intake, and diarrhoea for at least two consecutive days.

This chapter presents the major findings for each research objective, a discussion of the findings and the conclusions reached regarding the research question. As previously discussed in detail in Chapter Three, the aim of this exploratory, descriptive survey design was to explore relationships or differences between variables without determining cause. Thus, it was the purpose of this study to obtain quantifiable data in an objective and controlled manner in order to explore the complex relationships among the variables. No inference of causal relationships has been drawn. This chapter concludes with a discussion of the implications of those findings for policy and practice, and with recommendations for further research.

5.2 Major conclusions of the study

This section will first discuss the demographic results, which will be followed by a discussion of the five objectives of the study. The findings and a discussion of the research question are then presented.

5.3 Demographic characteristics of patients

The demographic information gathered in the study revealed that the median age of patients was 69 years, with the majority of patients being commenced on warfarin therapy in the 70-80 year category. The most common indication for warfarin was AF with almost half (49%) of all participating patients being commenced on warfarin for treatment of the arrhythmia. Thirty-eight per cent of patients were diagnosed with DVT/PE, with considerably fewer patients commenced on warfarin therapy post-myocardial infarct and heart valve replacements, resulting in the majority of participating patients being commenced on warfarin therapy as a result of cardiovascular disease (CVD).

According to a report by the Australian Institute of Health and Welfare (2006), the leading causes of the total burden of disease and injury in Australia in 2003 were cancers (19%) and CVD (18%). Hypertension, ischemic heart disease, stroke, diabetes and peripheral vascular disease were the leading specific causes of the cardiovascular burden (Australian Institute of Health and Welfare 2006).

The findings of this study reveal that the most common co-morbidity reported was hypertension (46%), followed closely by ischemic heart disease (37%), CCF (19%) and diabetes (18%). Furthermore, findings revealed that the average number of co-morbidities per patient was 1.8, with a maximum of seven co-morbidities recorded for any one patient. These findings are reflective of the report by the National Heart Foundation of Australia (2005), which suggests that 30% of the population over 25 years of age has hypertension and one in every six Australians is affected by CVD, with 67% of families impacted by this disease at present. It has been suggested that diabetes prevalence has more than doubled to over 3% self-reporting in 2001 (AusDiab cited in National Heart Foundation of Australia 2005), and heart failure has been described as a burgeoning

disease, although data concerning diagnosis, awareness and treatment remain poor (National Heart Foundation of Australia 2005).

Although there were significantly more males (62%) in this study than females (38%), this may be explained by the fact that males are more likely to be hospitalised for CVD than females (Australian Institute of Health and Welfare 2001). Furthermore, females have approximately 10 to 15 years' freedom from coronary heart disease compared with males, and consequently tend to be much older when symptoms develop (Mosca et al. 1997). The average weight of patients was recorded as 82.4 kilograms, with the maximum weight recorded at 146 kilograms. Because the body mass index was not measured in this study, it is not possible to determine the proportion of patients who were within normal limits, overweight or obese; however, the findings of this study indicate that 37% of patients weighed more than 85 kilograms. Recent statistics indicate that approximately 60% of adults in Australia over 25 years of age are overweight (National Heart Foundation of Australia 2005).

The significant co-morbid states that have been reported to increase instability in the INR include older age (>65-70 years), impaired cardiac or liver function, uncontrolled hypertension, gastrointestinal diseases, such as ulcers or haemorrhage, neurological defects, including stroke or cognitive deficits, renal insufficiency, excessive alcohol intake (Baker et al. 2004; Gallus et al. 2000; Pautas et al. 2006) and diabetes (Pautas et al. 2006). Additionally, patients diagnosed with CCF have been associated with an increased response to warfarin, thought to be due to hepatic congestion (Kayser 2005).

Of the concomitant medications taken by patients that were recorded, aspirin was the most commonly prescribed (29%), followed by paracetamol (21%), antibiotics (18%), amiodarone (13%) and clopidogrel (8%). Although the number of concomitant medications taken by each patient was not counted in this study, the majority of patients were commenced on warfarin for the treatment of AF, which most commonly affects persons of an older age (Ninio 2000). While the elderly population is most likely to benefit from anticoagulation therapy, they are also the most likely to be prescribed multiple medications and are at the highest risk for haemorrhage (Gullov, Koefoed & Petersen 1999; Howard et al. 2002). Moreover, patients with multiple co-morbidities and polypharmacy are at an increased risk of an unstable anticoagulant response (Gallus et al. 2000). All of the most commonly prescribed concomitant medications in this study are thought to cause instability in the INR or increase the risk of bleeding (Dale, Myhre &

Loew 1980; Ho & Brighton 2002: Hylek et al. 1998). Several studies have found that the majority of patients with chronic AF are prescribed drugs that can potentially interact with warfarin and as a consequence are at an increased the risk of bleeding (Anderson, Divers & von Hennigs 2005; Howard et al. 2002). For example, the most common drugs prescribed in a study by Anderson, Divers and von Hennigs (2005) included short-term drugs such as paracetamol, antibiotics and NSAIDS and long-term drugs such as glyburide (hypoglycemic sulfonylureas), allopurinol, levothyroid, SSRIs, amiodarone, lovastatin and cimetidine.

The issue of whether concomitant aspirin is of benefit to patients already receiving warfarin remains unresolved and controversial; however, it appears to be frequently prescribed especially in the ageing population who suffer co-morbid conditions and are commenced on warfarin therapy (Howard et al. 2002). Flaker et al. (2006), analysing data from the SPORTIF trials, suggest that the risks associated with the combination of aspirin and anticoagulation in AF patients outweighs the benefits. Flaker et al. (2006) found that there was no reduction in stroke, systemic embolism or myocardial infarction; however, there was an incremental rate of major bleeding of 1.6% per year, which is similar to the findings of previous studies (Hurlen et al. 2002; Levine et al. 2001; Shireman et al. 2004; van Es et al. 2002). However, contrary to these results, further studies have found that there are no additional risks with combined antiplatelet therapy and warfarin and that the risk of combined therapy remains unclear (Gullov, Koefoed & Peterson 1999; The Stroke Prevention in Atrial Fibrillation Investigators 1996). As the impact of the interaction between these drug combinations may not occur until after the patient has been discharged home, it appears prudent that patient education and close monitoring of the INR should be continued post-discharge from hospital, especially for the initial month of treatment and especially in patients receiving concomitant antiplatelet therapy.

Although the findings of this study indicate that 81% of discharge letters were written and a copy placed in the patient's medical records, it is not known whether those discharge letters were mailed in a timely manner or to the correct GP, whether they contained adequate information or even if that information was correct. However, in an email on 8 March 2007, the Hospital at Home Services Clinical Nurse Manager pointed out that for those patients who progressed through the Hospital at Home Services, a record of the patient's INR results and warfarin dosages was sent to each respective GP on discharge from the service (B. Farrelly 2007, pers. Comm., 8 March). The majority of patients

(93%) admitted into the hospital setting that were initiated on warfarin therapy were later transferred to the Hospital at Home Services and then discharged home to their GP for continued management. A considerable proportion of patients then experienced several transitions back and forth between institutions, the most being ten transitions for six patients.

The researcher did not initially set out to explore the transition process from the hospital to the community and back in detail; however, during the process of this study, it became clear that patient transitions are potentially a major concern in the management of patients receiving warfarin therapy. Several studies have reported that the likelihood of patients incurring an adverse event through medication error, injury, confusion associated with following instructions, poor compliance and continued ill health is greatly increased during the discharge transition period (Anderson, Divers & von Hennigs 2005; Forster et al. 2003; Jackson et al. 2004; Stewart & Pearson 1999). Furthermore, recent research has revealed that patients are not only at the highest risk of incurring a bleed during the initial few months of treatment (Linkins, Choi & Douketis 2003), but that instability of the INR is greatest during this time (Campbell et al. 2001; Vadher, Patterson & Leaning 1997). It would appear reasonable to assume that a patient who experiences multiple transitions between institutions while unwell might be confused or unclear as to the role of their warfarin therapy as opposed to a patient with a single transition. Furthermore, if discharge letters do not contain adequate information concerning the patient's treatment / medications or fail to reach the treating doctor in a timely manner, management of that patient may be compromised. It is clear that a seamless transition from institution to community and back is essential for optimal management of each patient receiving warfarin. A study conducted by Peterson et al. (2006), exploring the problems related to sub-optimal management of prescribed medications among patients discharged from acute hospital care, made several recommendations to improve the transition process. These strategies will be further discussed later in the chapter.

In summary, the demographic findings of this study appear to reflect the general trends and health of Australians in relation to the increased number of elderly persons to commence warfarin therapy for the treatment of AF and the continued incidence of hypertension, diabetes, CCF and ischemic heart disease. The findings also indicate that multiple co-morbidities were common, again especially in the elderly population who were commencing warfarin for AF. The majority of patients commencing warfarin

therapy were initiated in the hospital setting. The continued management of those patients defaulted almost wholly to the GP on discharge, with a small percentage only remaining in the care of the OPD in the study hospital. Finally, the transition period of patients from the hospital to the community and back was identified as a potential problem in the management of patients receiving warfarin therapy.

The following sections will present the major conclusions related to each objective in the study. This will then be followed by a discussion related to the research question.

5.4 Objective One: Assess frequency of INR monitoring during initial five months of warfarin therapy in both hospital and community setting

This section will first present a discussion of the frequency of INR monitoring during the initial month of treatment, followed by a discussion regarding the frequency of INR monitoring during months two to five.

5.4.1 Frequency of INR monitoring during initial month (30 days) of warfarin therapy

The findings of the survey found that the mean number of INR tests recorded during the initial month of warfarin therapy was 12.8. The minimum number of INR tests was 3 and the maximum was 28 tests conducted during that time. For those patients who incurred an initial episode of over-anticoagulation during the first month of treatment the mean number of INR tests conducted was 14.7. For those patients who incurred more than one episode of over-anticoagulation during the first month of treatment the mean number of INR tests conducted was 16.2, indicating that there was a marginal non-significant increase in INR testing when a patient incurred an episode of over-anticoagulation. However, it is not known whether the frequency of INR monitoring was diligent prior to the episode of over-anticoagulation or increased as a consequence of the high INR result. There were twelve patients who incurred two episodes and one patient who incurred three episodes of over-anticoagulation during the initial month of treatment.

National published guidelines and authors of previous studies suggest the frequency of INR monitoring on initiation of warfarin therapy should include daily monitoring for the

first week of therapy or until two consecutive therapeutic values have been reached, followed by INR tests two to three times per week for the first and second week thereafter. This is then followed by periodic INR checks every four to six weeks depending on the patient's stability, with more frequent tests conducted if dose adjustment occurs or if the patient incurs an acute illness or potentially interacting drugs are commenced (Ansell et al. 2001; Gallus et al. 2000; Ho & Brighton 2002; Horton & Bushwick 1999). It is estimated that if a doctor follows these guidelines, a minimum number of 12-14 INR tests would be conducted during the first month of treatment, provided no adverse events and only minimal dose adjustments occurred.

The findings of this study indicate that while the average frequency of monitoring during the initial month of treatment was consistent with the minimal suggested frequency of previous studies (Ansell et al. 2001; Horton & Bushwick 1999) and the above mentioned guidelines, there were 90 (31%) patients who had less than 11 INR tests during the initial month of treatment. The reasons for this are unknown, but previous studies suggest frequent laboratory testing presents a burden for many patients, especially the older patients, and non-compliance and confusion of management by patients remains an issue (Cheah & Martens 2003; Garcia et al. 2005; Kimmel et al. 2007).

However, given that the findings of this study also indicate that the vast majority of episodes of over-anticoagulation and major bleeds occurred during the initial month of therapy, these episodes and bleeds might well have been prevented if management of the warfarin therapy were more closely monitored. It appears from the findings of this study and previous studies that the initial month of treatment is the crucial period of warfarin management. White et al. (2007) and Hylek & Singer (1994) found that INR control during the first 30 days of treatment is predictive of subsequent INR control, while patients with poor INR control at six months are more likely to have poor long-term INR control. While an important goal of warfarin therapy is to balance patient safety with patient compliance, cost and convenience (Horton & Bushwick 1999), close INR monitoring especially during the initial month of treatment has the potential for doctors and nurses to pick up out-of-range INR values early and make appropriate dose adjustments. Therefore, it is advocated that strategies for more frequent INR monitoring during the initial month of warfarin therapy are instigated, although these must remain within the boundaries of clinical practicality. These strategies will be discussed further under implications for policy and practice.

5.4.2 Frequency of INR monitoring during months two to five after initiation of warfarin therapy

The findings of this study revealed that the average frequency of INR monitoring per month for months two to five was 2.9 with a median of 2.4, a minimum of 0.5 and a maximum of 11.0 times. Thus, the average time between INR readings in this study was 10.3 days. There were several patients in this study whose warfarin was ceased shortly after the initial month and prior to 46 days. These patients had intensive INR monitoring conducted prior to the cessation of their warfarin treatment, indicating that perhaps there was some difficulty in stabilising their INR prior to its cessation, hence more frequent monitoring intervals.

Results of the study conducted by The Newcastle Anticoagulation Study Group (1998) were similar in that the authors found that the frequency of INR tests conducted ranged from one to eleven per month on average. The median time between INR readings was seven days. However, the findings of this study included months two to five only and not the initial month of treatment while the study conducted by The Newcastle Anticoagulation Study Group (1998) included the frequency of monitoring within six months of discharge. As such, one could assume that the frequency of monitoring might have been higher in this study if the initial month of treatment had been included.

The findings of this study are in contrast with a study by Ansell et al. (2007), who conducted a large retrospective, multi-centre study in the United States, Canada, France, Italy and Spain, to evaluate the quality of anticoagulation management in patients with chronic non-valvular AF and receiving vitamin K antagonists. The study included 1,511 randomly selected patients from representative Routine Medical Care (RMC) practices in the US, Canada and France and Anticoagulation Clinic Care (ACC) practices in Italy and Spain. The median INR monitoring intervals were between 20-21 days in all countries in the study, except Spain, where the median time interval was 32 days irrespective of INR values. However, the study also found that the average monitoring interval was between six and 12 days in the three RMC samples when the INR was above 3.5 or below 1.5 (Ansell et al. 2007).

Quantitative data from the doctor questionnaires in this study found that 98% of respondents reported that they would increase the frequency of monitoring for a time after

if dose adjustment was required while 93% reported that they would also increase the frequency of monitoring if there was a change in the patient's health, lifestyle or medications. These findings suggest that monitoring in this study was increased if the INR value was outside the target range, which is similar to the findings of the study by Ansell et al. (2007). While the frequency of monitoring in this study was well within the national published guidelines recommended by Gallus et al. (2000) and Baker et al. (2004), the reason for the overall high frequency of monitoring compared to the above studies is not known.

In summary, the findings revealed that the average time intervals between INR measurements in months two to five after initiation was approximately 10 days, which is similar to those reported by The Newcastle Anticoagulation Study Group (1998) but much higher than the intervals reported by Ansell et al. (2007). There is a paucity of literature on the frequency of INR monitoring in the community, especially in the Australian community, making comparisons few. As a result, future research exploring frequency of monitoring, cost-effectiveness and outcomes after the initial month of therapy would be invaluable.

5.5 Objective Two: Determining number of episodes of over-anticoagulation during initial five months of warfarin therapy, specifically in first month compared with subsequent months of treatment

The findings of this study revealed that there were 190 single episodes of over-anticoagulation among 294 patients during the study period. While 117 (40%) patients incurred at least one episode of over-anticoagulation, there were 177 (60%) patients who did not incur any episodes of over-anticoagulation. Of the 117 patients who did incur an episode of over-anticoagulation, 65% patients incurred one single episode, 21% patients incurred two episodes, 7% incurred three episodes, 2% incurred four episodes, and 3% incurred five episodes. Finally, 2% patients incurred six and seven episodes of over-anticoagulation respectively.

Of the episodes reported by the 117 patients who incurred at least one episode of over-anticoagulation during the study, 82 (70%) episodes occurred during the initial month of

treatment. The median number of days from initiation of warfarin therapy to the initial episode of over-anticoagulation was 14 days.

As discussed in Chapter Two, because there is a close relationship between the INR and the risk of bleeding, an INR>4.0 places the patient at a greater risk and rises sharply when the INR>5.0 (Baker et al. 2004). Furthermore, previous studies have suggested that older patients who incur an episode of over-anticoagulation take longer to return to a safe INR level, exposing them longer to potential bleeding risks (Fihn et al. 1996; Gurwitz et al. 1992; Hylek et al. 2001). Moreover, it has been suggested that patients who incur an INR above the therapeutic range are associated with an increased mortality rate at 60 days (Koo et al. 2004). Most importantly, the main cause of excessive anticoagulation in the study conducted by Koo et al. (2004:1560) was attributed to 'errors in drug monitoring'. Previous studies have also indicated that the patient is at the highest risk of a bleed during the initial three months of therapy (Baker et al. 2004; Campbell et al. 2001; Linkins, Choi & Douketis 2003; Vadher, Patterson & Leaning 1997). The findings of this study indicate that the patient is at a much higher risk of incurring a bleed during the first three months of therapy, but further suggest that the patient may be at the highest risk of an adverse event during the initial month of therapy and that inadequate monitoring may significantly contribute to the cause. The implications of these findings suggest that policies regarding close management during the initial month of treatment are of overriding importance and strategies to implement these policies are recommended to be put in place.

Additionally, the findings of this study revealed that the mean INR result recorded in those patients who incurred an episode of over-anticoagulation was 5.1, indicating that many of those patients were at significant risk of a bleed (Baker et al. 2004). Four patients were recorded as having an INR≥11.0, which were the highest INR results recorded in the study. While one patient suffered a major bleed 11 days after the event, all patients required re-hospitalisation and treatment or further medical attention at the time. Furthermore, findings revealed that there was a likely cause/s for each of the INR≥11.0, namely, acute illness, concurrent profuse diarrhoea, the administration of antibiotics and a lack of INR monitoring, and that these were likely to be the cause/s of the elevated INR of patient # 1. The causes of the episode of over-anticoagulation of patient # 2 were likely overdosing and a lack of INR monitoring. Patient # 3 admitted to being confused as to dosing and subsequently overdosed her/himself and patient # 4, by his/her own

admission, had a substantial increase in alcohol intake during the two days prior to the INR test being conducted. These findings suggest that all of these episodes of over-anticoagulation could be attributed to a specific likely cause/s and potentially avoided. This indicates that further patient education regarding alcohol intake, overdosing and the importance of regular monitoring is essential while medical education concerning the importance of more frequent monitoring, the effect of medication interaction and the presence of intercurrent illnesses in patients receiving warfarin is also warranted.

The most likely cause/s overall of episodes of over-anticoagulation in this study were drug interactions, inappropriate dose adjustment, patient compliance issues and decreased oral intake for a variety of reasons. The researcher acknowledges that the cause of many episodes of over-anticoagulation were unknown due to inadequate information available to the researcher. It is not known whether, if this information were available, a cause would be identifiable or not. Thus, further studies that are able to ascertain this are essential in order to determine the potential to prevent episodes of over-anticoagulation.

The circumstances surrounding the over-anticoagulation in the above four patients are congruent with the quantitative data obtained from the doctor questionnaires for this study. When asked 'What barriers do you face, if any, in the management of warfarin therapy?', a large percentage of doctors reported that the lack of patient compliance and a poor understanding of warfarin therapy, along with medication interactions, were common issues that they faced. Furthermore, of those doctors (52%) who replied 'yes' or 'sometimes' to the question 'Are you able to predict or foresee instability of an INR?' an overwhelming proportion reported that a change in medication/drug interaction was the most common contributing factor to instability in the INR. Patient compliance issues, a change in diet or an acute illness were reported as the next most common factors.

Furthermore, the findings of previous studies (Howard et al. 2002; Panneerselvam et al. 1998; Wittkowsky & Devine 2004) also found a change in medication, especially the administration of antibiotic therapy in the four weeks prior to a change, to be a common precipitant associated with an episode of over-anticoagulation. Moreover, several studies conducted both in Australia and overseas (Arnsten, Gelfand & Singer 1997; Bajorek et al. 2007; McCormack et al. 1997; Tang et al. 2003) have found that patients' knowledge of warfarin therapy is generally poor. Subsequently, several studies (Arnsten, Gelfand & Singer 1997; Beyth, Quinn & Landefeld 2000; Campbell et al. 2001) have reiterated that

patients who have a poor understanding of warfarin therapy are more likely to be non-compliant and the implications of these findings will be further addressed in Section 5.10.

Inappropriate dose adjustment also appeared to be a precipitant for an episode of over-anticoagulation. The researcher judged the inappropriateness of dose adjustments based on the age-adjusted warfarin initiation protocol used in the study hospital (Roberts et al. 2003). The findings of this study may reflect the same reasons suggested by Bajorek et al. (2007), who found that current information for the initiation and ongoing management of warfarin therapy might not be available to doctors. A lack of current information available, particularly to GPs, who wanted practical and interactive advice for dealing with certain situations, was found to be lacking in a study by Bajorek et al. (2007) which examined the perspectives of clinicians, allied health professionals and patients in the use and management of warfarin conducted in Sydney, NSW. It was acknowledged that, although there are published guidelines available, GPs need practical information on how to apply data obtained from clinical trials to individual patient situations. The study highlighted an important issue here. The significant responsibility of the management of warfarin therapy, particularly after the patient has been discharged from the hospital, has been defaulted to the GP (Bajorek et al. 2007). Strategies for the dissemination of practical information and implementation of advice for clinicians will be discussed further in the following sections.

In summary, the findings of this study reveal that the majority of episodes of over-anticoagulation occurred during the initial month of treatment. The mean INR result recorded was 5.1, indicating that many patients were at a significantly increased risk of incurring a bleed (Baker et al. 2004). Although not all patients who incurred an episode of over-anticoagulation suffered a bleed, many required further medical attention with or without re-admission to hospital. This ongoing exposure to potential complications and recurrent hospital stays with subsequent debts incurred have the potential to impair the restoration of the patient's health and cause ongoing stress to both the patient and their family. The highest INR results recorded were equal to or greater than 11.0 and all of these could be attributed to a likely cause/s, suggesting that many episodes of over-anticoagulation are potentially preventable with closer monitoring, improved warfarin management and improved patient education.

5.6 Objective Three: Determining number of major bleeds during initial five months of treatment

The most common and potentially devastating complication associated with warfarin therapy is bleeding (Baker et al. 2004; Gallus et al. 2000; Levine, Raskob & Hirsh 1989). The number of major bleeds and minor (but clinically significant) bleeds recorded in this study were based on the definition used by Gallus et al. (2004) listed in Section 1.6.

There were seven (2.3%) patients who incurred a major bleed during the study period, with three of those seven incurring the bleed while the INR was within the range of 1.9-3.4. Although all seven patients incurred the major bleed during the initial three months of treatment, six of the seven patients incurred this bleed during the initial month of treatment. While 7 of a total of 17 minor (but clinically significant) bleeds occurred during the initial month of therapy, all 17 of these bleeds occurred during the initial 96 days of warfarin therapy. There was one bleed that was classified under 'other' bleeds. Overall, a total of 52% of all bleeds occurred during the initial month of therapy. These findings are similar to those reported in several previous studies in predicting an increased bleeding risk rate during the initial three months of treatment (Fihn et al. 1993; Landefeld & Goldman 1989; Linkins, Choi & Douketis 2003; Palareti et al. 1996;). However, the findings of this study suggest that the initial month of treatment may expose the patient to a higher risk of bleeding than the second and third months, which is consistent with the findings of the study by Landefeld and Beyth (1993). The authors found that the risk of a bleed was approximately 10-fold higher during the initial month of therapy than after the initial year of therapy (Landefeld & Beyth 1993). The researcher acknowledges that the definition of a major or minor (but clinically significant) bleed and 'Other' bleeds in this study may not be congruent with definitions made in previous studies, thus it is difficult to make precise comparisons across studies.

Although 2.3% of patients in this study incurred a major bleed, only the events of the first five months were recorded. However, the findings appear similar to those in Landefeld and Beyth's (1993) study who recorded that an average risk for major bleeding was approximately 3% per year, with bleeding occurring most often in the gastro-intestinal tract, soft tissues and the urinary tract. Results of this study revealed that of the seven patients who incurred a major bleed, three involved the gastro-intestinal tract, two involved the urinary tract and one involved soft tissue and respiratory tract respectively.

Of the 18 (6.1%) patients who incurred a minor (but clinically significant) bleed or 'other' bleed, 10 (55%) were associated with an episode of over-anticoagulation. Thus, the overall proportion of patients to incur a bleed during the study period was 25 (8.5%). The findings of this study indicate that 56% of those patients who incurred a bleed did so when their INR>4.0. This is consistent with previous studies (Campbell et al. 2001; Oake et al. 2007). A meta-analysis conducted by Oake et al. (2007) found that overall 44% (95% CI 39-49) of haemorrhages occurred when the INR was above the therapeutic upper range of 3.0 and 3.5. The study also found that half of all events did not occur when the INR was outside the therapeutic range (Oake et al. 2007), which supports the report by Landefeld and Goldman (1989) who proposed 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. However, overall, Oake et al. (2007:1593) found 'that improved anticoagulation control could decrease the likelihood of almost half of all adverse events associated with anticoagulants taken orally'.

In summary, while the findings of major bleeding in this study are similar to those of previous studies, the outcome of the assessment of bleeds in this study suggests that the patient may be at the greatest risk of a bleed during the initial month of treatment as opposed to during the initial three months of treatment. This indicates that efficacious INR control and frequent INR testing is of paramount importance for the avoidance of adverse effects and to obtain optimal benefits and safety for the patient receiving warfarin therapy. The implications of these findings and strategies for these outcomes will be discussed further below in the chapter.

5.7 Objective Four: Assessing patient's understanding of warfarin therapy, general health and degree of compliance prior to episode of over-anticoagulation while receiving warfarin treatment

The discussion relating to this objective is divided into three sections. First, the level of the patient's understanding of warfarin therapy will be discussed, followed by the degree of compliance by the patient prior to an episode of over-anticoagulation. Finally, the health status of patients shortly prior to an episode of over-anticoagulation will be discussed.

5.7.1 Level of patients' understanding of warfarin therapy

It has been suggested by several authors that a sound understanding of warfarin therapy and subsequent good patient compliance is essential to realise the full benefits of warfarin therapy (Arnsten, Gelfand & Singer 1997; Bajorek et al. 2007; Cheah & Martens 2003; Gallus et al. 2000).

The majority of patients in the study were initiated on warfarin therapy in the study hospital and a large proportion of those patients were transferred through the Hospital at Home Services. In a personal conversation on 25 January 2007, the Clinical Nurse Manager of the Hospital at Home Services and G.P. Liaison Service at the study hospital revealed that patients being admitted to the Hospital at Home Services received a comprehensive educational program from the nursing staff. (B. Farrelly, 2007 pers. Comm., 25 January). The program began when the patient was visited for the first time in their home and continued until the patient was discharged from the Hospital at Home Services.

According to the Clinical Nurse Manager, a 'Warfarin Therapy Education Checklist' is given to each staff member to provide guidance to the topics that are to be covered in the educational sessions (B. Farrelly, 2007 pers. Comm., 25 January). Those topics include the following:

1. Why are you on warfarin?
2. What is your target INR?
3. How often should you have your INR done?
4. What can change your INR?
5. What do you need to look out for when you are on warfarin?
6. When should you take your warfarin tablets?
7. What do you do if you miss a dose?
8. What effect does your diet have on your INR?
9. Should you drink alcohol while you are taking warfarin?
10. Do you keep a record of your INR and warfarin doses?
11. When do you need to contact your doctor?

12. Who else should know you are on warfarin?

13. Is it safe to use warfarin during pregnancy?

Furthermore, warfarin information sheets written by the clinical pharmacists in the pharmacy department are available (Siebert n.d.) on the wards for those patients being commenced on warfarin for most indications. It was assumed by the clinical pharmacist that these pamphlets were given to each patient by the nursing staff prior to the patient's discharge from hospital. The pamphlets include such information as what warfarin is and how it works, why the patient is taking warfarin, blood test information, how and when warfarin should be taken, any unwanted effects of warfarin and other relevant information that the patient should be aware of (Siebert n.d.).

This study indicated that 78% patients interviewed reported that their understanding of why they had been started on warfarin therapy was because their blood needed to be 'thinned' to prevent clots from forming. A much lower proportion, however, were able to make an association between their diagnosed disease state and the need for the prevention of formation of clots. Furthermore, when patients were asked whether they understood how warfarin worked, 74% reported that they had a basic understanding and explained it by suggesting that the warfarin 'thinned' the blood. A small proportion of patients did not appear to understand how warfarin worked at all.

An alarmingly low 29 (40%) patients only reported that they were aware of the main side effects of warfarin. When asked by the researcher to identify them, only 20 of the 29 patients mentioned bleeding as the main side effect. When asked by the researcher whether they were aware of what signs and symptoms of bleeding caused by warfarin were, only 46 (63%) patients reported that they knew the signs and symptoms. Furthermore, when asked to identify them, not one patient could identify all covert and overt signs and symptoms of bleeding and only 8% and 13% of patients could name four and five symptoms respectively. Additionally, of the proportion of patients who reported that they experienced some signs and symptoms of bleeding, only 58% reported that they informed their treating doctor.

Results of the study also revealed that of the patients interviewed, only 52 (71%) kept a record of their INR results and warfarin dosages. Furthermore, when an overall estimation of the proportion of patients keeping a record of their dosages and INR tests was made,

findings showed that only 61% of patients did so. However, not all information provided correlated with data later checked with patient medical records, with 14% of these patient's data failing to correlate with the checked data. That is, the patients wrote down an incorrect dosage and/or INR results, indicating that there was some misunderstanding by the patient of the instructions received from the doctor.

In a personal conversation on 25 January 2007, the Clinical Nurse Manager of the Hospital at Home Services and the GP Liaison Service revealed that when staff provide information on why the patient is on warfarin, the condition is related to the treatment, for example, if the indication for warfarin is atrial fibrillation, the disease process is explained and related to the reasons for the treatment. The staff highlighted the all-important main side effect of warfarin, that is, bleeding. Emphasis is placed on describing the signs and symptoms of bleeding the patient should look for and when to report them to their GP. The patients are encouraged to keep a record of their dosages and INR results and are provided with a booklet in which to do so. Lastly, the patient is informed of when next to make an appointment to see their GP for INR monitoring and dose adjustments, with only four to seven days' worth of warfarin tablets given to each patient on discharge from the study hospital (B. Farrelly, 2007 pers. Comm., 25 January).

While 81% of patients reported that they understood why the dose of warfarin might change, an overwhelming majority reported it was because the INR had changed. Conversely, only 57% of patients were aware of the length of time the warfarin therapy was required. Additionally, 74% patients reported that they received the same brand of warfarin every time from the chemist. However, 22% patients were uncertain of this requirement due to the fact that they were either still in hospital or had not yet filled a prescription. The findings of this study reflect those of a recent survey conducted by Bereznicki et al. (2006) in southern Tasmania where the authors found that only 17% of 243 patients indicated a good (80%) level of warfarin knowledge based on the validated questionnaire used.

In summary, the findings of this study indicate that the patient's understanding of warfarin therapy was average regarding why warfarin was commenced, how warfarin works and why the dosage may change, and also the patient's practice of keeping a record and obtaining the same brand from the pharmacist each time. However, the findings indicated that patients' knowledge concerning the main side effects of warfarin, what signs and symptoms of bleeding to look for and when to inform the treating doctor was

very poor. Patient knowledge concerning bleeding, what signs and symptoms to look for and when to report them to the doctor are key aspects of warfarin therapy that are essential for the patient to be aware of. In some instances, patients reported that they knew the answer to questions asked, but when asked to clarify their answers further were unable to do so, causing the researcher to believe that they did not have a good understanding at all, but instead were inclined to answer 'yes' to each question asked. Overall, these findings are consistent with previous studies (Bereznicki et al. 2006; Campbell et al. 2001; Cheah & Martens 2003; McCormack et al. 1997; Tang et al. 2003; The Newcastle Anticoagulation Study Group 1998), indicating that generally patient's knowledge of their warfarin therapy remains poor. This will be further discussed in Section 5.10.

Cheah and Martens (2003), who conducted a descriptive study concerning patient knowledge in Columbus, US, surmised that the reasons contributing to the inability of many patients to manage their own warfarin therapy on discharge from hospital could be attributed to the patient's acute state of illness along with tiredness, depression, pain or discomfort and the possibility of being under the influence of medications while an in-patient. Cimprich 1992 cited in Cheah and Martens (2003:95) suggest that while in hospital, there are many environmental distractions that may not allow the patient to fully comprehend the information given and mental effort is required to sustain attention and suppress these distractions in order to take in new information and learn.

Bajorek et al. (2007) found in their qualitative study, which was based on the analysis of group interviews, that both health professionals and patients alike felt that the existing written information on warfarin therapy regarding the everyday management of issues that appear to cause the most problems, that is, drug interactions, complementary medicines and dietary vitamin K intake, was less than satisfactory. The supply of the standard 'little blue warfarin booklet' was considered insufficient as a stand-alone measure and both interactive verbal and written information were required in a paced manner, with the opportunity for patients to verify their understanding at a later time. This concept was reiterated by Cheah and Martens (2003), who proposed that patients' understanding of terms and information provided must be followed up with questions to clarify their level of knowledge. The above issues relating to the existing written information and the delivery of that information to patients have important implications for this study, which will be discussed further in the following sections.

5.7.2 Degree of compliance by patient prior to an episode of over-anticoagulation

The findings of this study revealed that the degree of compliance by patients was varied. When patients were interviewed to determine their degree of compliance prior to an episode of over-anticoagulation, findings indicated that a large proportion of patients achieved very reasonable compliance in several areas, and these findings will be discussed below. However, when information was conveyed to the researcher through other data collection means, that is, through the checking of medical records, conversing with doctors or speaking with patients each month via the telephone, there was evidence to suggest that compliance with warfarin therapy was less than satisfactory in many areas.

The proportion of patients interviewed who informed the doctor of all medications taken was reported as large (96%), as was whether the patient informed the doctor of the commencement of any new tablets (96%) and the proportion of patients who reported that they took their warfarin at the same time each day (99%). The increased use of occasional medicines taken and reported to the doctor by the patient (90%) and the proportion of patients who reported that they never missed a dose (84%) was reasonable, but not as large. Nevertheless, these findings indicate a large proportion of patients reporting good compliance with therapy in these areas of patient management. However, these findings conflict with the quantitative data obtained from the doctor questionnaires as to the barriers faced in the management of warfarin therapy. A frequently reported barrier reported was that of patient compliance, in particular, patients taking OTC medications without informing their doctor, missed doses, not presenting for regular INR tests, incorrect dosage taken and not being contactable to inform them of INR results and new dosages. Furthermore, the use of OTC medications and patients' understanding of warfarin and subsequent compliance were common factors reported by doctors to cause instability in the INR.

Although there was a large proportion of patients with good compliance in the above areas of patient management, the researcher noticed less than satisfactory compliance among several patients when general information regarding warfarin therapy was obtained each month when contacted. For example, a patient ceased taking his/her warfarin for no obvious reason three to four days prior to seeing the GP, several more patients adjusted their own dosages without the GP's knowledge, and one patient took

less than the instructed dosage for an extended period of time because he/she had 'run out' of the prescribed amount. Another two patients ceased their own warfarin therapy, deeming the cost was too high to continue, but failed to inform their doctor. When the researcher checked the medical records on completion of data collection, it was found that several more patients had acknowledged to the GP, when attending for an INR test, that they had missed a dose or several doses. Several patients failed to attend the surgery for frequent or regular INR tests, with one patient having only four INR tests conducted during the five-month study period. Furthermore, there were 11 (42%) of 26 patients who reported that there had been a major change in their normal eating habits in the week prior to the episode of over-anticoagulation, and that the change had been a substantial increase in alcohol intake.

Conversely, there were several incidents reported by patients where they had attempted to be proactive in their warfarin management and had found it to be difficult. For example, three patients had requested a copy of their INR results from their GPs and were refused, the GP citing no time, a further three patients were unsure of when to present for the next INR test and another patient requested a warfarin information booklet and was told there were none available. One patient was unhappy with the lack of reassurance and information given concerning some bruising that was evident, while another patient experienced difficulty in contacting the GP to obtain the INR results and dosage required.

The findings also showed that while most patients were informed of their warfarin dose by telephone by either the doctor or surgery staff members, with 99% of patients reporting that those instructions were either '*very easy*' or '*easy*' to follow, three of those patients took incorrect dosages and subsequently incurred an episode of over-anticoagulation which required medical attention with/without readmission to hospital. Additionally, as mentioned above, 14% of the records of INR results and warfarin dosages provided by patients failed to match those of the medical records kept by the hospital/s or GP when checked. These findings indicate that many patients were taking a different dosage of warfarin to what their doctor believed them to be taking.

Moreover, two patients failed to inform their treating doctors of significant changes in their health status and required readmission to hospital and acute medical intervention. Patient # 1, after being discharged home into the care of the Hospital at Home Services, was readmitted to hospital within days with internal bleeding (Hb=68 g/L) and melena. The patient had been experiencing nausea, decreased appetite and passing black tarry

stools for the previous three days, but because he/she was not aware of what signs and symptoms of bleeding to look for, did not report it to the attending nurses who visited the patient on a daily basis. Upon conducting an endoscopy, the patient was found to have six active bleeding ulcers. Patient # 2 suffered a substantial knock on his/her arm, which resulted in a subsequent minor (but clinically significant) bleed and was readmitted to hospital as a result, where the patient was found to be over-anticoagulated.

Although the findings of this study concerning the degree of compliance appear satisfactory to high in several areas when patients were questioned, it appears that compliance was less than satisfactory in other areas, and in some areas the findings conflicted with the findings reported by doctors. It appears that patients were not compliant with the therapy, were not aware of the importance of being compliant or were not aware of the consequences of their non-compliance. Several studies suggest that compliance with therapy or medical treatment is enhanced by knowledge and an understanding of the drug, its benefits and its side effects (Arnsten, Gelfand & Singer 1997; McCormack et al. 1997; Lloyd & Rodgers 1994). This evidence appears congruent with the findings of this study in that as the basic level of knowledge of warfarin by patients in this study was reported as generally poor, particularly concerning the major side effects of warfarin, signs and symptoms of bleeding and when to report them to the doctor, it is reasonable to suggest that this may have impacted on the degree of compliance. Furthermore, Pautas et al. (2006) found that such factors as impaired cognitive function and/or dementia in the elderly can contribute to poor compliance. In this study, a large proportion of patients were greater than 70 years, which may have been a contributing factor.

Kimmel et al. (2007) found that patients have substantial difficulties with maintaining adequate compliance with warfarin therapy and that this poor compliance has a significant effect on anticoagulation control. Although patients in the study by Kimmel et al. (2007) were constantly reminded of the importance of adherence to their warfarin therapy, their findings demonstrated poor adherence in both the initiation and maintenance phase, with 40% of patients experiencing clinically significant levels of poor adherence.

Additionally, Kimmel et al. (2007) reported that even moderate levels of non-compliance with therapy are clinically important. For example, missing one to two doses of warfarin per week would lead to a two-fold increase in the odds for a sub-therapeutic INR,

independent of other factors, such as demographic factors, interacting medications and diet. Although over-adherence to therapy was associated with over-anticoagulation in their study, taking extra warfarin was less common than under-dosing (Kimmel et al. 2007). The issue of non-compliance by patients will be further discussed below.

5.7.3 Health status of patients shortly prior to an episode of over-anticoagulation

It has been suggested that an intercurrent illness, or a change in bowel habit or diet such as acute diarrhoea, vomiting or an increased fever or temperature may influence the INR (Baker et al. 2004; Gallus et al. 2000). Thus, the purpose of assessing the presence of an intercurrent illness in patients prior to an episode of over-anticoagulation was to further assess the level of warfarin knowledge and the degree of compliance among patients.

Only a small proportion of patients (13%) reported experiencing diarrhoea for at least two consecutive days during the study period, with a known 45% of those patients reporting it to the doctor. An even smaller proportion of patients (3%) reported experiencing vomiting for at least two consecutive days, with one patient failing to report it to the doctor. This one patient was experiencing other significant complaints during this time, and was being closely monitored by the doctors; however, he/she failed to mention experiencing any nausea or vomiting to the treating doctor. According to the patient, while the nausea was persistent, the vomiting was intermittent and of small amounts. The patient was eventually diagnosed with invasive adenocarcinoma of the stomach and consequently, warfarin was ceased.

The proportion of patients who reported an increased temperature or fever was small (8%), with less than half of those patients reporting it to their doctor, and there were 18 (22%) patients who reported a newly diagnosed illness during the study period, with 16 of those patients reporting it to their treating doctor. These findings indicate that if patients in this study incurred an intercurrent illness, acute diarrhoea, vomiting or an elevated temperature, approximately only half reported it to their treating doctors. Of those patients who failed to report health-related complaints to their doctor, three had serious complaints which resulted in re-admission to the study hospital, requiring acute medical attention.

In summary, a high proportion of patients interviewed reported that they complied with the requirements concerning other medications and warfarin therapy prior to an episode

of over-anticoagulation and approximately half of the patients who reported an intercurrent illness informed their treating doctors. Despite this, there were frequent incidents where several patients failed to comply in many other areas. This may have been a result of their general knowledge of warfarin therapy being low and thus the importance of compliance not being uppermost in their minds. These findings correspond to the findings by Kimmel et al. (2007), who found that patients struggle to maintain compliance both early and later in treatment, even when constantly reminded.

In conclusion, it is clear from the findings of this study that there remains a gap in the level of knowledge of patients receiving warfarin therapy and subsequently in the degree of compliance achieved. These findings should encourage clinicians to both evaluate and implement new strategies to improve compliance and hence anticoagulation control. Strategies that have been suggested include the implementation of anticoagulation clinics and patient self-management (Oake et al. 2007). Bajorek et al. (2007) found that patients wanted detailed information that included the reason for taking warfarin, how it works and how dose adjustments are made, and the reasons behind observed phenomena such as bruising and variable INR results. Patients also wanted information tailored for older patients and expressed dissatisfaction with the lack of precautionary information about drug interactions.

Cheah and Martens (2003) suggested, as a result of their study, that emphasis be placed on six key areas of patient education. That is, the patient must be taught about the action of warfarin in terminology that is understood by them, the patient should be instructed about potential bleeding and what signs to look for and potential medication interactions with warfarin. Finally, further instructions should be given regarding the consistency of maintaining a regular diet and all of these instructions should be tailored to the learning needs of the elderly. Moreover, in the study by Bajorek et al. (2007), hospital pharmacists suggested that education alone was not adequate for older patients and they required more support through the use of mobile community-based services while GPs recommended community liaison services such as home visits for drug monitoring, counselling and further education. Additionally, the sub-optimally formatted, mass-produced written information presently distributed was deemed unsatisfactory and additional counselling, especially developed for the elderly, such as larger type for printed materials and videos, was warranted, with the individual patient's needs being catered for (Bajorek et al. 2007). There was a need for coordinated education for both patient and their carers, with

verification of the patient's understanding of warfarin (Bajorek et al. 2007; Cheah & Martens 2003).

Additionally, Bajorek et al. (2007) found that patients perceived a lack of confidence regarding warfarin therapy and generally felt fearful of taking the drug. They felt somewhat abandoned in their management of warfarin because of limited access to their GP, a lack of information provided by community pharmacists and lack of ongoing support, advice and education available. It has been suggested by hospital pharmacists that raising the profile of warfarin and dispelling some of the myths surrounding it by utilising alternative modes of education such as television campaigns and an array of health and medical-based television programs would allay some of the fears held by patients (Bajorek et al. 2007).

Although an education program exists in the hospital where the majority of patients were initiated on warfarin and thereafter in the Hospital at Home Services, it is clear from the findings of this study that many patients were not able to grasp or retain that information. This is especially evident in the lack of knowledge regarding the main side effect of bleeding and the associated signs and symptoms. Similarly, patients interviewed by Bajorek et al. (2007) expressed that even those who received comprehensive education in the hospital setting found that it was difficult to apply that knowledge once they were discharged. The patients believed that face-to-face accessible support and advisory services in the community setting were necessary, but they did not feel that GPs alone could manage this (Bajorek et al. 2007). The implications of the GP managing this alone will be discussed in the following section.

Finally, Bajorek et al. (2007:179) suggest 'that very simple measures, such as disseminating information to patients and GPs, and the participation of allied health professionals, may have some far reaching effects in terms of improving the use and management of warfarin'. It appears from these recent studies (Bajorek et al. 2007; Cheah & Martens 2003; Kimmel et al. 2007) and the findings of this study that there exists a significant gap in the level of knowledge and compliance of patients. Therefore, there is an urgent need for the implementation of new strategies with the use of new technologies to disseminate the information, with further research conducted to evaluate its effectiveness. These strategies and new techniques will be discussed in detail in the following sections.

5.8 Objective Five: Assessing current trends and concepts in medical management of patients receiving warfarin therapy in hospital and community setting

The initiation of consensus guidelines and the delivery of practice incentive programs to community doctors in recent times has been made in an attempt to provide strategies for doctors to deliver high-quality management to improve anticoagulation control and minimise the incidence of adverse events in patients receiving warfarin therapy.

One such program is that initiated by the National Prescribing Service, which in 2005 disseminated an outreach educational program titled 'Using antithrombotics: maximising benefits; minimising risks' to the majority of GPs in South Australia (National Prescribing Service Limited, accessed 2 February 2005). Results of this study indicate that the proportion of GPs who attended any of these programs in 2005 was small (22%). The reason for such a small attendance is not known. Evaluation of the reasons why many GPs did not attend would be invaluable in the design and delivery of future educational programs.

Results indicate that the proportion of doctors, both hospital-based and community-based, who routinely set an INR target prior to commencement of warfarin therapy was very large (97.9%), with 82.5% of all doctors reporting that they would alter the normal target range in certain situations. The most commonly reported situations included those patients who had undergone a valve replacement, on specialist advice, for the elderly and frail patient, depending on the clinical profile of the patient and those patients deemed to be at an increased risk of bleeding. These findings are congruent with the consensus guidelines published by the Australasian Society of Thrombosis and Haemostasis, which suggests that an INR target range should be set and is best kept between 2.0-3.0 for most clinical indications, but may be higher for certain patients and situations (Gallus et al. 2000). The optimal INR target range for patients with mechanical heart valves is still being debated (Stein et al. 2001). Recently a meta-analysis of eligible studies concerning the incidences of thromboembolic and bleeding events in patients with mechanical heart valve prostheses during vitamin K antagonist therapy conducted by Vink et al. (2003) found that a target above 3.0 was beneficial.

While the findings of this study revealed that the majority of doctors set a target range between 2.0-3.0, which is in accordance with the guidelines, there were some who lowered the range to 1.5. Although it has not been proven that a reduced target range of 1.5-2.0 reduces the bleeding risk for a patient (Kearon et al. 2003), it has been suggested that it is likely to lead to some reduction in the effectiveness of therapy (Gallus et al. 2000). For those patients diagnosed with AF, the relative risk for a stroke doubles when the INR is 1.7, triples when the INR is 1.5, sextuples when the INR is 1.3 and reaches 18 times the relative risk when the INR is normal (Hylek et al. 1996). Despite this, Gallus et al. (2000) suggest that for some elderly patients of 75 years or older, a target range of 1.5-1.9 may offer an acceptable level of safety while maintaining some benefit against bleeding. In stark contrast to this concept, Pautas et al. (2006) suggest that a fear of over-anticoagulation by clinicians should not be a reason to lower the INR<2.0 in patients with acute venous thromboembolism or AF; instead, management should be conducted in a coordinated manner between educated patients and family and physicians with early detection of potential adverse events.

Few doctors in this study reported an upper INR range that was higher than 4.0. Those who did so recommended it for the 'older' style valves and aortic valve replacements. The British Society for Haematology recommended that because evidence remains incomplete regarding the INR range for prosthetic valves, it is prudent to retain a target range between 2.5-3.5 for most 'low risk' prosthetic valves and a higher range of 3.0-4.5 for older models which are more thrombogenic, provided there are no other contraindications (Baglin & Rose 1998). The findings of this study revealed that of those doctors who specified a set target for valve replacement, approximately half reported a range of 2.5-3.5, which is consistent with the recommenced guidelines. According to the recommendations suggested by Baker et al. (2004), an INR level that balances the therapeutic goal with the risk of bleeding on an individual basis is a key element to optimising warfarin therapy.

Although the majority of doctors reported that they set the INR target range for each patient, a substantially lower proportion (55.7%) reported that they determined the duration of therapy. These findings are similar to the proportion of those patients interviewed who were aware of the length of time their warfarin therapy was required (57.6%). Although many of these patients were initiated in the hospital setting and not by the GP, the specialist or the GP on discharge from the hospital failed to inform the patient

of the duration of their warfarin therapy or the patient failed to hear the information and retain it. Ho and Brighton (2002) suggest that the duration of therapy should be determined in advance so that it can be tailored to each individual.

The findings of this study revealed that the majority of hospital-based doctors utilised an established algorithm more often than they used their own clinical judgment when initiating patients on warfarin therapy. This may have occurred due to the large proportion of hospital-based doctors (medical interns) who completed the question (42.5%). It could be assumed that as a medical intern their general knowledge and experience of initiating patients on warfarin therapy may not have been as developed or in-depth as that of a Consultant, Registrar or GP. Moreover, the hospital environment is geared for the education of its staff. An established algorithm provides a format for safe guidelines for the initial few days of warfarinisation. Further findings showed that GPs in the community used their own clinical judgment more often than they utilised an algorithm or both. These findings were in contrast with a prospective observational assessment of anticoagulation care in 98 office-based practices and three hospital-based clinics conducted by Hylek (2003) in the US, which reported that 89% of the practices participating in the study used a warfarin dosing algorithm and 27% of practices had a protocol for bridging with low molecular weight heparin. Comments made by some of the GPs in this study indicated that they found algorithms too restrictive and that other important factors needed to be taken into account when determining dosage. Additionally, patients being initiated on warfarin in the community by GPs were more likely not to require rapid anticoagulation and thus a more gentle approach could be adopted.

There were 87.2% of doctors who reported that they routinely assessed each patient for the risk of bleeding prior to commencement of warfarin therapy and 96.6% of doctors who informed their patient of the risk of bleeding on commencement of warfarin therapy. Conversely, the proportion of doctors who reported that they re-evaluated the patient's harm:benefit ratio for warfarin during the course of their therapy was less than expected, with only 79.3% reporting that they did so. Published guidelines advise that a complete assessment of a patient's risk:benefit ratio, including the risk of bleeding, is an essential part of initiating warfarin therapy and should also be reassessed routinely after initiation on an annual basis (Baglin & Rose 1998; Baker et al. 2004; Campbell et al. 2001; Ho & Brighton 2002). Therefore, it could be expected that the proportion of doctors who routinely assessed each patient for the risk of bleeding prior to commencement of therapy

and re-evaluate the harm:benefit ratio during the course of therapy would be 100%, even among those doctors who reported that they seldom initiate patients on warfarin therapy or those hospital-based doctors treating patients re-admitted during the course of their therapy.

The recent study conducted by Bajorek et al. (2007) in Sydney, NSW, found that cardiologists required GPs to play an active role in the decision-making process of initiation of treatment to aid them in the assessment and documentation of a patient's suitability for warfarin therapy. The authors also found that there is a need for more information for GPs and hospital-based doctors concerning, specifically, the risks factors in the elderly population, to support the decision to initiate warfarin therapy. This includes the systematic documentation of risk assessments, especially the strict pathophysiology of stroke in the presence of AF, more effective communication with the appropriate clinicians to assist in the selection of suitable treatment for individual patients and a wider dissemination of pertinent clinical trial evidence to provide the rationale for specialists. The findings of the study by Bajorek et al. (2007) are reflective of a previous Australia-wide survey conducted by Peterson et al. (2002) who assessed the attitudes of GPs, cardiologists and physicians towards the use of antithrombotics for the prevention of stroke in non-valvular AF patients. The authors of the study found that there was scope for improvement in doctor's knowledge concerning use of anticoagulation therapy in non-valvular AF and an awareness of findings of recent clinical trial information. Peterson et al. (2002) found that GPs were likely to overestimate the reported risk of a major bleed, while cardiologists were more likely to choose the recommended treatment. Bajorek et al. (2007) and Peterson et al. (2002) suggest that the process of dissemination of clear guidelines and focused education on risk factors may help clarify the perceived under-utilisation of warfarin, particularly in the elderly population.

An important component of assessing a patient for warfarin therapy is to complete the individual's history by assessing their blood picture. A baseline blood test that includes an INR, Hb, aPTT, albumin, platelet count and liver function test has been suggested as prudent prior to commencement of therapy (Baglin & Rose 1998). Approximately 80% of doctors overall in this study reported that they would order baseline blood tests prior to the commencement of warfarin therapy. Of these 80%, 96% of hospital-based doctors reported that they would do so while only 72% of GPs reported that they would do so. Of those doctors who reported that they would conduct baseline blood tests prior to

commencement of therapy, the most common blood tests reported were coagulation studies (26.5%) and liver function tests (26.5%), followed by a full blood count (25.9%) and urea and electrolytes (13.3%). Data collected for each participating patient in this study showed that 91.1% of patients had a pre-dose INR conducted, 97.6% had a pre-dose Hb conducted, 97.2% had a pre-dose platelet count conducted and 94.5% of patients had a pre-dose serum albumin conducted. Although only 72% of GPs reported that they would conduct pre-dose blood tests, the majority of patients in this study were initiated in the hospital system, this being the likely reason for the high proportion of patients to have these blood tests conducted. Additionally, it has been suggested that patients with a baseline elevated INR will be more sensitive to warfarin (Kayser 2005). In this study there were only three patients with an INR>1.3 and there were no episodes of over-anticoagulation among those patients.

Although there have been several scoring systems developed (Beyth, Quinn & Landefeld 1998; Gage et al. 2006; Kuijer et al. 1999), the proportion of doctors who reported that they use a scoring system to stratify the risk of bleeding was extremely small (1.4%), indicating that this concept is not widely known or used. Several doctors reported that it was not a concept they were familiar with, while others said that they were familiar with the concept but had not found a scoring system that was proven to be reliable; however, several doctors had expressed an interest in using one if one was available. Gage et al. (2006) suggest that the quantification of the risk of haemorrhage could vastly improve the use of anticoagulant therapy in three ways. First, it could be improved by aiding in patient selection to help determine whether the benefits of warfarin outweigh the risks. Second, it could be improved by allowing clinicians to monitor the therapy more closely in those at-risk patients, and third, by aiding in the identification of which asymptomatic patients with a supratherapeutic INR should receive vitamin K. The establishment of a bleeding risk scheme may, in turn, contribute to overcoming the fear of haemorrhage by doctors, particularly for the elderly population, and the subsequent reluctance of clinicians to initiate some patients on warfarin therapy (Bajorek et al. 2002; Enis 1997; O'Connell et al. 2000).

Of the doctors who reported that they did not inform the patient of the bleeding risk prior to commencement of therapy (3.4%), four out of five reported that they did not initiate patients on warfarin and relied on other health professionals, such as pharmacists, to inform patients. The remaining doctor reported that he/she did inform the patient during

the course of treatment. It would appear from these findings that the majority of those GPs who did not initiate patients on warfarin, albeit a very small number, assumed that other health professionals informed the patient.

The low proportion of patients who were aware of the main side effects of warfarin and the signs and symptoms of bleeding associated with warfarin conflicts with the high proportion of doctors who reported that they inform the patient of the risk of bleeding. It would appear from these findings that the information provided by the doctors on this specific subject is failing to impact on the patient. Patients receiving warfarin therapy must know that bleeding is the main side effect of warfarin therapy and they must also be aware of the associated signs and symptoms of bleeding (Cheah & Martens 2003; Ho & Brighton 2002). These findings are consistent with previous studies, suggesting that patients feel the present method of dissemination of material and the content of that information requires re-evaluation (Bajorek et al. 2007; Cheah & Martens 2003). These findings support the critical need for new strategies to be instigated and subsequently re-evaluated, which are discussed below.

In identifying what education the patient receives regarding their warfarin therapy that doctors are aware of, the researcher found that generally it was varied and inconsistent. Nevertheless, all doctors who completed the questionnaire were of the belief that patients received some degree of education in some form, if not from them, then from another source. Hospital-based doctors thought the bulk of information/education came from the clinical pharmacist in the hospital, with some doctors reporting that they spoke with patients themselves, while a very small proportion of hospital-based doctors were not aware of what information was provided. The majority of GPs reported that they provided most of the information verbally during patient visits with the provision of a pamphlet or booklet. However, several GPs thought that patients initiated in the hospital received education as an in-patient and others directed the patient to the community pharmacist or the Internet. It appears from these findings, coupled with above findings regarding warfarin education/information provided, that there is an assumption by health professionals, at least in part, that other colleagues are providing the education to the patient. Although little detail was gained from the questionnaires concerning the format of the information provided, it appears that the majority of the information was on a mass-produced basis and not tailored to the individual.

Additionally, both hospital-based doctors and GPs were asked whether they commonly discuss six lifestyle factors known to impact on the INR with the patient. The proportion of doctors to discuss the consistency of dietary intake of vitamin K with the patient was relatively low (62.5%), considering changes in dietary intake was mentioned frequently as a contributable cause to instability of the INR. Likewise, the proportion of doctors who discussed minimising alcohol intake and avoidance of binge drinking was again relatively low with 65.9% and 69.4% respectively, with 70.8% of doctors reporting that they discussed a reduction of activities with considerable risk, including risk of falls in the elderly population. However, there was a large proportion (93.0%) of doctors who reported discussing the reporting of any new medications/OTC/alternative medications to the patient's doctor. It would appear from these and previously reported findings of this study that medication interactions are of a major concern to both hospital-based doctors and community-based doctors in the management of warfarin therapy. The implications of these findings are important and will be discussed further in Section 5.10.

The proportion of doctors who reported that they are able to predict or foresee the instability of an INR, or were sometimes able to do so, was 52.0%. The finding of a relatively low proportion of doctors who reported that they are able to predict instability in the INR results is inconsistent with several previous studies, which suggest that the instability of the INR is very much predictable (Beyth, Quinn and Landefeld 1998; Ho & Brighton 2002; Merli 2002; Panneerselvam et al. 1998). A change in the patient's health or medications should prompt more frequent monitoring of the INR, with patient education and understanding of signs and symptoms of blood loss an essential component for the overall efficient management of patients (Ho & Brighton 2002). Merli (2002) suggests that instability in the INR is predictable and that eventually it becomes routine with experience and knowledge. The author suggests that every episode of over-anticoagulation should be investigated and is usually caused by one of three factors: the introduction of a concomitant drug that enhances the effect of warfarin, incorrect dosing or the occurrence of a dispensing error (Merli 2002).

Doctors in this study reported that the most common contributing factors to the cause of instability in the INR were as follows: first, a change in medications, such as antibiotics, amiodarone, OTC medications or polypharmacy; second, a perceived lack of patient compliance; and third, a change in the patient's diet or an episode of acute illness. The presence of co-morbidities, age, alcohol intake and changes in the patient's lifestyle were

also all considered contributing factors. These results are reflective of the contributing factors named in the above studies.

Even though 47.9% of doctors reported that they were not able to predict instability in the INR, a relatively large proportion of doctors (89.5%) reported that they would attempt to identify the cause of an INR>4.0. Again, medications/drug interactions were considered the main cause, followed by changes in the patient's diet, including alcohol intake, patient compliance and the general health of patients. Furthermore, 96.3% of doctors reported that they would attempt to correct the cause of an INR>4.0 if identifiable, suggesting that a large proportion of doctors believed that there was not only an identifiable cause for the INR>4.0, but that the cause was rectifiable if identified. These findings suggest that perhaps more doctors think that instability of the INR may be predictable, at least to some extent, than was reported in the study, since otherwise one would question why so much time and effort would be invested in an irresolvable problem.

When doctors were asked whether they considered an increased INR above 4.0 to be an acceptable occurrence during warfarin therapy, 62.7% thought that it was not acceptable. Of the 37.3% of doctors who thought that it was acceptable, however, over two-thirds reported that although it was a common occurrence, it should be acted on, especially if the target range was below 4.0. A large proportion of doctors (98.6%) reported that they would adjust the dose if the INR were above the target range. There were 93.7% of doctors who reported that, if there were a change in the patient's health, lifestyle or medications, they would increase the frequency of INR monitoring for a time after. It appears from these results that doctors are very much aware of the dangers associated with an increased INR above 4.0 and the importance of adherence to the preset INR target range, as discussed above in this chapter.

Finally, doctors in this study were asked 'What barriers do you face, if any, in the management of warfarin therapy?'. According to Bungard et al. (2000), there have been few surveys that have directly asked doctors about the perceived barriers they face with anticoagulation. Thus, it was important in this study to identify those barriers in order to ascertain the day-to-day difficulties encountered by doctors, in particular GPs, as they appear to bear most of the day-to-day management of the patient receiving warfarin. The findings of the study revealed that 89.3% of doctors perceived that they faced barriers in the management of warfarin therapy. The most common barriers reported concerned

patient compliance and patients' general understanding of warfarin therapy, polypharmacy and medication interactions and unexplained fluctuations in the INR, along with the risk of bleeding and the age of patients. The overall process of warfarin management was reported as time-consuming and cumbersome, using the present system, with a lack of POC monitoring available.

The findings of this study were in contrast with the barriers reported in the survey by Peterson et al. (2002), who reported such variables as active gastrointestinal bleeding, history of daily falls and previous intracranial haemorrhage. However, the authors suggested that these factors were perhaps uncommon as they are clearly contraindications to anticoagulant therapy and it may have been that other more common factors such as dementia, advancing age, poor control of INR and patient's distance from the surgery were ranked slightly lower as barriers but are more important in practice. Nevertheless, the overall response of doctors was that anticoagulation is underutilised in patients with AF and the availability of portable INR monitors would assist with the management of these patients (Peterson et al. 2002).

In summary, the findings revealed that overwhelmingly the majority of doctors set a target range prior to the commencement of warfarin therapy, with the most common target range set 2.0-3.0 for most conditions and 2.5-3.5 for most valve replacements, which is consistent with the target range set in previous studies (Ansell et al. 2007; The Newcastle Anticoagulation Study Group 1998). A small proportion of doctors set the lower range to 1.5 while a small proportion set the upper range to 4.0 or above for various conditions. While approximately only one half of the doctors determined the duration of therapy, the proportion of doctors who routinely informed the patient of the risk of bleeding and assessed each patient for the risk of bleeding prior to commencement of therapy was high. The proportion of doctors who reported routinely reassessing the harm:benefit risk ratio periodically throughout therapy was less than was expected at 79.3%. The use of a scoring system to estimate bleeding risks was extremely small, indicating that only two of 147 doctors utilised such a system.

The majority of hospital-based doctors reported using an established algorithm to initiate patients on warfarin therapy while the majority of community-based doctors reported using their own clinical judgment. While a high proportion of hospital-based doctors reported taking base-line bloods prior to commencement of therapy, a lower proportion of community-based doctors reported doing so. The perceived delivery of education by

doctors appears to be inconsistent and varied, resulting in an apparent concern with the level of understanding of warfarin therapy and the subsequent degree of patient compliance. Although approximately only half of the doctors reported that they could predict instability in the INR, the majority reported that they would investigate an INR>4.0 and attempt to identify the cause, suggesting that perhaps the majority of doctors believe there was an identifiable cause. Additionally, while a little over one half of the doctors thought that an INR>4.0 was not acceptable, the majority of the remaining doctors said that they would act on it if it was persistent and the majority of doctors reported that they would adjust the dose.

In conclusion, these results indicate that the risk of bleeding, especially in the elderly population, interaction with medications and subsequent instability in the INR, the level of patient understanding of warfarin and ensuing patient compliance appear to be the major concerns of doctors in the management of warfarin therapy. The reason for the relatively low proportion of doctors who reported to periodically re-evaluate the harm:benefit ratio of the therapy and the duration of therapy is not known. Because the majority of patients were initiated on warfarin therapy in the hospital setting, it may be perceived by the community-based doctors that the reassessment of the harm:benefit ratio and the duration of therapy is the responsibility of the specialist, even though the day-to-day management of the warfarin has been defaulted to the GP. It is not known whether the GPs in this study felt there was a lack of relevant and practical information available to them in order to make these decisions or not, or whether a lack of communication between specialists, hospital-based doctors and cardiologists initiating warfarin therapy exists. The education received by the patient that the doctors were aware of appears to be varied and inconsistent, indicating that this is a likely adjunct to the poor level of understanding of warfarin by the patient. It would also appear that, in the present health care climate, the time available to spend with patients is severely limited, further indicating that the participation of all healthcare professionals, such as pharmacists and hospital-based and community-based nurses, in the ongoing management of patients receiving warfarin is essential. This conclusion is significant for policy and practice, which will be discussed further in Section 5.10.

5.9 Research question

The research question was 'Are episodes of over-anticoagulation potentially preventable or unforeseeable?' In order to address the research question, each covariate of interest thought to impact on an episode of over-anticoagulation was statistically analysed using survival analysis (Cox Regression Model) and the Poisson model to estimate the predictive value and the incidence rate ratio respectively for an episode of over-anticoagulation, using SPSS version 15.0 and Stata version 7.0. The results of these analyses are discussed first. Finally, the findings in respect of all five objectives and the conclusions relating to the research question are evaluated and discussed.

5.9.1 Gender and episodes of over-anticoagulation

It appears from a review of the literature that there is a paucity of information concerning the significance of patients' gender in warfarin therapy. The consensus guidelines recommended by the Australasian Society of Thrombosis and Haemostasis do not mention gender as a variable to consider when initiating patients on warfarin therapy (Baker et al. 2004; Gallus et al. 2000). Therefore, it was important to this study to quantify the effect of gender as a predictor of an episode of over-anticoagulation. Results revealed that gender was not a significant factor (Sig.=0.668). The results of previous studies by Garcia et al. (2005) and Horton and Bushwick (1999), however, suggest that females generally require less warfarin than males.

The study by Garcia et al. (2005) found that a significant association between warfarin dose and gender existed and that females required less warfarin than males. The authors of the study found that at any given age, the mean weekly dose for females was 4.5 mg less than that for males, and that lower initiation and maintenance doses should be considered for the elderly, with females requiring the lowest doses. The authors of the study postulated that the explanation for females requiring less warfarin than males might lie in the differences in mean body size or hepatic fat content, or in the intrinsic differences in the metabolism of warfarin (Garcia et al. 2005). Because there is a paucity of extant literature, further research regarding the association between episodes of over-anticoagulation and gender would be invaluable to clarify this issue.

5.9.2 Age and episodes of over-anticoagulation

The significance of age as a contributing factor to an increased risk of bleeding complications has been researched frequently in previous studies. While it was important to this study to attempt to clarify the significance of age as a contributing factor to an episode of over-anticoagulation, it was not the intention of the researcher to investigate the direct association between age and the risk of a bleed.

Survival analysis using a Cox Regression model was utilised to quantify the effect of age as a predictor of an episode of over-anticoagulation. Results were significant and indicated that for each year of age a patient was 1.02 times more likely to incur an episode of over-anticoagulation. Furthermore, the incidence rate ratio for an episode of over-anticoagulation was increased by 1.01 for each year of age while holding all other variables in the model constant.

These research findings are consistent with those found by several previous studies (Dobrzanski et al. 1983; Garcia et al. 2005; Redwood et al. 1991; Sheperd et al. 1977). All of these studies found that elderly patients on average were more sensitive to the effects of warfarin therapy; however, the reasons remain unknown. The study by Garcia et al. (2005) confirmed earlier findings by Wynne et al. (1996) and van der Meer et al. (1996) who suggested that there was a significant correlation between age and dosage requirements. Garcia et al. (2005) suggested that for each additional year of age, the weekly dose declined by 0.4 mg and that the recommended daily starting dose of 5 mg would be excessive for up to 82% of females and 65% of males who were more than 70 years of age.

While several early studies suggested that there is an increased risk of bleeding complications associated with age (Jick et al. 1968; Kernohan & Todd 1966), more recent studies have failed to find an increased risk in bleeding complications (Fihn et al. 1993; Fihn et al. 1996; Kagansky et al. 2004) and instead have suggested an increased sensitivity to warfarin. The authors of these studies found that warfarin therapy can be safely administered to the elderly population with careful monitoring and attention to the INR. It was thought that the intensity of warfarin and the level of prothrombin time (INR) were strong predictors of the risks of bleeding rather than age itself (Fihn et al. 1993; Fihn et al. 1996; Kagansky et al. 2004).

To date, approximately only one half of the many studies conducted have found a significantly increased risk of bleeds associated with age (McCrory et al. 1995). At present, however, it is generally acknowledged that particular care is required when treating elderly patients receiving warfarin therapy, and while it remains unclear whether they are at a greater risk of bleeding or not, there appears to be a significant relationship between age, dose requirements and INR level. This suggests that as this study's findings revealed, age is a significant predictor of an episode of over-anticoagulation and close and frequent monitoring of the INR coupled with less intensive dosage is required.

5.9.3 Antibiotics and episodes of over-anticoagulation

Panneerselvam et al. (1998) suggest that a recent change in medications is one of the most common precipitants associated with an episode of over-anticoagulation. Medications that are used long term for the management of diseases are controllable; however, when short-term medications such as antibiotics are introduced, management can become difficult (Horton & Bushwick 1999). Because antibiotics are usually prescribed short-term, it has been suggested that clinicians might not be aware of the potential of antibiotics to interact. However, significant changes in the INR may occur even within the two-week duration of a typical antibiotic course (Howard et al. 2002).

Although not all antibiotics have been proven to cause an increase in the INR, all antibiotics taken by patients in this study were included in the analysis. The results revealed that as a predictor of an episode of over-anticoagulation occurring, antibiotics was a strong factor. The results also indicated that the incidence rate ratio for an episode of over-anticoagulation would be expected to rise by 1.81 if a patient received warfarin and antibiotics concomitantly.

These results are consistent with the results of previous studies (Glasheen 2005; Hirsh et al. 2003; Howard et al. 2002; Udall 1965; Wiese & Cosh 1999) that found that the INR increased with various antibiotics. Antibiotics are considered to be the most common group of drugs that interact with warfarin (Horton & Bushwick 1999; Panneerselvam et al. 1998) and, interestingly, in this study doctors reported similar issues with antibiotics, indicating that this remains a problem today.

However, Glasheen (2005) suggests that it is almost impossible to differentiate between the effects of an antibiotic and the effect of the patient's illness on the INR. Those factors

associated with acute infections and changes in hepatic and renal function are all thought to impact on the body's response to warfarin. Therefore, while various antibiotics are known to increase the INR, Glasheen (2005) suggests that vigilant monitoring of the INR in any acutely ill patient, especially if they have been commenced on antibiotics, is prudent.

5.9.4 Amiodarone and episodes of over-anticoagulation

Amiodarone is an efficient and frequently used drug in the management of supra-ventricular and life-threatening ventricular arrhythmias (Sanoski & Bauman 2002). Although the interaction between amiodarone and warfarin is well documented and occurs in almost all patients receiving this combination (Howard et al. 2002), it was important in this study to quantify its effects in order to assess whether doctors were aware of the interaction and adjust the warfarin dose accordingly.

According to Howard et al. (2002), the interaction between amiodarone and warfarin and the subsequent increase in the INR is particularly worrying because there a strong possibility that the INR will increase within three to four days after commencement of therapy or, conversely, it may be delayed for up to three weeks. Furthermore, the potential for affecting the INR continues following discontinuation of amiodarone for weeks to months after. This is of concern because it requires extended intensive INR monitoring and careful adjustment of dosage for the patient (Howard et al. 2002).

The findings of this study were consistent with previous studies (Howard et al. 2002; Kerin et al. 1998; Sanoski & Bauman 2002), indicating that amiodarone has a strong ability to potentiate the effect of warfarin with a resultant episode of over-anticoagulation. The results indicate that a patient taking amiodarone and warfarin concomitantly is 2.049 times more likely to incur an episode of over-anticoagulation.

Furthermore, amiodarone was a commonly prescribed medication in this study and these results indicate that although the interaction is well documented, doctors are either not aware of its interaction or few doctors take its effect on warfarin into account when determining the warfarin dosage. The findings of this study indicate that the combination of amiodarone and warfarin remains a problem in the management of patients receiving warfarin and further education is required to clarify the dosage and frequency of monitoring required.

5.9.5 Paracetamol and episodes of over-anticoagulation

Because paracetamol has no antiplatelet effect or potential to induce gastrointestinal bleeding, it has become the preferred choice of analgesia and is commonly prescribed (Chan 1995); however, whether paracetamol potentiates the effects of warfarin remains unclear. Gebauer et al. (2003) postulates that there remains considerable conjecture surrounding the issue because a plausible explanation of the mechanism has not been put forward and the interaction has been observed inconsistently in clinical practice.

Previous studies by Kwan, Bartle and Walker (1999), Gadisseur, van der Meer and Rosendaal (2003) and Smith, Aljazairi and Fuller (1999) respectively found no significant increase in prothrombin times after varying doses of paracetamol and an oral anticoagulant were administered. However, while the studies conducted by Kwan, Bartle and Walker (1999) and Smith, Aljazairi and Fuller (1999) used warfarin, the study by Gadisseur, van der Meer and Rosendaal (2003) used phenprocoumon.

The findings of this study indicate that paracetamol, as a predictor of an episode of over-anticoagulation, was marginal only (Sig.=0.032). Conversely, studies conducted by Hylek et al. (1998) and Parra, Beckey and Stevens (2007) respectively reported a significant increase in the INR value after concurrent paracetamol. The study by Hylek et al. (1998) found that paracetamol was independently associated in a dose-dependent manner with an increased INR value and that for an intake of 9,100 mg/week or more of paracetamol, the odds of having an INR above 6.0 increased 10-fold over those taking no paracetamol. However, a limitation noted 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.

A more recent prospective, randomised, double-blind placebo-controlled trial by Parra, Beckey and Stevens (2007) reported similar results, with the authors finding a significant interaction between the daily use of 2-4 grams of paracetamol and warfarin. The authors found that more than half of their patients in the study taking paracetamol developed an increased INR of between 0.6-2.8 by week four of the trial, with 83% of patients' INR results returning to normal on cessation of paracetamol. However, significant limitations also existed in this study, due to its small sample size (n=36) and early termination of the trial (Parra, Beckey & Stevens 2007).

In summary, while the current study found that paracetamol was a marginal predictor of an episode of over-anticoagulation, studies by Hylek et al. (1998) and Parra, Beckey and Stevens (2007) reported a clinically significant interaction between warfarin and paracetamol. These results conflict with other studies conducted by Kwan, Bartle and Walker (1999) and Gadisseur, van der Meer and Rosendaal (2003). It appears that all studies had limitations, which may have impacted on the results and thus, the interaction between warfarin and paracetamol remains an important but unresolved clinical issue for many patients with co-morbidities who require this analgesia while receiving warfarin. Gebauer et al. (2003) suggests while the issue remains unresolved, patients should not exceed 2 grams per day of paracetamol and that more frequent monitoring of the INR should be conducted if patients begin taking doses greater than this amount. Thus, further research that explores paracetamol as an interactive medication with warfarin would be valuable.

5.9.6 Frequency of monitoring during initial month of treatment and episodes of over-anticoagulation

A study by White et al. (2007) indicated 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, and patients with poor INR control during the initial six months of treatment were highly likely to have poor INR control in the long term. A study by Hylek and Singer (1994) suggested that INR control during the initial 30 days of treatment was predictive of subsequent control, making the initial month after commencement of warfarin therapy the most pivotal period of treatment during which to establish good INR control. Subsequently, recent studies have reported improvement in INR control and subsequent clinical outcomes due to improved frequency of INR testing along with the dissemination of further education (Bond & Raehl 2004; Ezekowitz et al. 1999; Hambidge 2002; Jackson et al. 2004; Menendez-Jandula et al. 2005).

The findings of this study indicate that the majority of episodes of over-anticoagulation occurred during the initial month of treatment, as did the majority of major bleeds. Thus, the frequency of INR monitoring was assessed in this study during the initial month of warfarin therapy to determine the effect of monitoring as a predictive factor for an episode of over-anticoagulation. The results indicated that the frequency of INR

monitoring conducted was a very significant factor (Sig.=0.000), suggesting that a patient is likely to incur an episode of over-anticoagulation 1.098 times more often if frequency of monitoring is inadequate. Furthermore, after applying the Poisson model, results indicated that the incidence rate ratio for an episode of over-anticoagulation is likely to increase by 1.08 while holding all other variables constant in the model, if frequency of monitoring is reduced (P>[z]=0.000).

While it has been proposed that more frequent monitoring, sometimes weekly throughout therapy for some patients, has been suggested (Ho & Brighton 2002), a significant goal of warfarin therapy is to find a balance between patient safety and patient compliance, discomfort, cost and the inconvenience of ongoing frequent monitoring (Horton & Bushwick 1999). Frequent monitoring in the present-day health care system often presents as a significant burden for many patients on warfarin therapy, especially the elderly population. They are often more dependent on others for transportation and may be challenged by mobility and health issues which impede attendance at the doctor's surgery or laboratory (Garcia et al. 2005). There is growing evidence to indicate that POC measurement by patients in their home improves outcomes, primarily because of the unlimited access, convenience and opportunity for increased frequency of INR testing (Ansell et al. 2001; Ezekowitz et al. 1999; Menendez-Jandula et al. 2005; White et al. 1989). It is also thought that self-management increases patients' knowledge of warfarin and subsequently improves compliance. Furthermore, self-management allows the patient to assume more responsibility for their own health, which in turn leads to improvement in the patient's self-worth, and awareness of the importance of compliance (Ansell et al. 2001; Menendez-Jandula et al. 2005). However, it is clear that POC monitoring or self-management is not suitable for all patients who are commenced on warfarin therapy. Therefore, those patients who do not fit the criteria for such schemes must have access to alternate facilities that are able to provide increased monitoring, especially during the initial month of treatment, along with ongoing and practical information to enhance their knowledge and compliance. These findings are significant because the findings of this study suggest that if episodes of over-anticoagulation are to be prevented, INR monitoring during the initial month of treatment needs to be frequent. Yet this has the potential to impact on the daily lives of many patients, especially those who are burdened with immobility and lack of transport. These results are pivotal to the implications of

future policy and practice for all health care professionals and this will be discussed below.

5.9.7 Congestive Cardiac Failure (CCF) and episodes of over-anticoagulation

Co-morbidities, like concomitant medications, have the potential to impact on warfarin sensitivity and dosage (Kayser 2005). It has been reported that one such co-morbid condition is CCF (Fihn et al. 1993), especially in those patients with decompensated CCF, because it may lead to hepatic congestion or oedema and an altered anticoagulant response (Demirkan et al. 2000; Hylek et al. 2001). Subsequently, Demirkan et al. (2000) advised that caution should be exercised during the use of anticoagulants in patients with this co-morbidity.

It appears that the interaction between CCF and warfarin is not widely known as there was limited information found in the literature. Thus, it was important for this study to quantify the effect of CCF as a predictive covariate on episodes of over-anticoagulation, particularly as CCF has been recently described as a 'burgeoning' disease in Australia (National Heart Foundation of Australia 2005).

The findings of this study revealed that CCF is a significant predictor of episodes of over-anticoagulation (Sig.=0.003). The results also indicated that the incidence rate ratio for an episode of over-anticoagulation would be expected to increase to 1.93 when a patient has CCF and receiving warfarin therapy, if all other variables in the model were constant.

In summary, as CCF was the third most common condition reported in the co-morbidities recorded in this study, it would be prudent for clinicians to initiate caution when commencing patients on warfarin therapy, especially patients with decompensated CCF. Furthermore, due to the limited information available regarding the increased sensitivity to warfarin in decompensated CCF patients and the results of this study, it is suggested that further research into the area would be invaluable and wider dissemination of information regarding this phenomenon would be prudent.

5.9.8 Diarrhoea for at least two consecutive days and/or decreased oral intake and episodes of over-anticoagulation

It has been widely accepted that a significant reduction in dietary vitamin K, for any number of reasons, is likely to potentiate the effect of warfarin, especially in sick patients (Gallus et al. 2000; Hylek et al. 1998). Because of the multiple factors that can influence the effect of warfarin, it can be difficult to identify diet as the cause of an altered INR. A diet that completely excludes vitamin K, such as liquid weight reduction diets, or acute illnesses, such as gastroenteritis with profuse vomiting and/or diarrhoea, or fever that lasts for over 24-36 hours, are highly likely to impact on the INR (Kayser 2005). Furthermore, in particular patients treated with antibiotics and intravenous fluids with no added vitamin K supplements and patients with fat malabsorption may also suffer increased INR results (Hirsh et al. 2003).

Black (1994) reported increased INR results after having a bout of giardiasis himself while Smith, Aljazairi and Fuller (1999) reported a case where a patient experienced six episodes of an increased INR in association with bouts of diarrhoea and a decreased appetite. Hylek et al. (1998) found diarrhoea and decreased oral vitamin K consumption placed patients at a higher risk for elevated prothrombin times in a prospective case-control study involving case patients (n=93) and control patients (n=196). However, a limitation of the study by Hylek et al. (1998) may have existed in that although the results reported a significantly (P=0.001) reduced intake of vitamin K, the actual amount of vitamin K was not assessed and bias may have been introduced through memory recall by patients when asked about their diet in the previous days.

The findings of this study revealed that those patients experiencing diarrhoea for at least two consecutive days while receiving warfarin therapy were 4.538 times more likely to incur an episode of over-anticoagulation (Sig.=0.000). These results are consistent with the results of the studies by Black (1994) and Smith, Aljazairi and Fuller (1999). Additionally, the results revealed that a patient experiencing a decreased oral intake for any reason while taking warfarin was almost six times more likely to incur an episode of over-anticoagulation (Sig.=0.000). However, the researcher acknowledges that it was highly probable that a decreased oral intake or diarrhoea alone was not the sole cause of an episode of over-anticoagulation. As previously mentioned by Kayser (2005), it is difficult to isolate and identify a single cause as other factors, such as concurrent medications, acute illness, combinations of both or other factors, may impact on the

anticoagulant control. Nevertheless, although this study was a descriptive study, and it was not the intention of the researcher to establish a cause-and-effect relationship but rather to explore relationships or differences between variables without determining cause, these results strongly suggest it would be prudent for treating doctors to be alerted to a potential increase in the INR results in patients who suffer either diarrhoea for at least two consecutive days or a decreased oral intake for any reason.

5.9.9 Serum albumin and episodes of over-anticoagulation

It is widely acknowledged that patients with low serum albumin levels (<30 g/L) may be more sensitive to warfarin and incur increased INR results if dosage is not adjusted (Horton & Bushwick 1999; Roberts et al. 2003). However, it was important in this study to determine the proportion of patients with a low albumin commenced on warfarin therapy who incurred an episode of over-anticoagulation and to analyse serum albumin, as a covariate, to determine the best predictive model for episodes of over-anticoagulation.

The findings of this study revealed that 55% of 31 patients with a serum albumin less than 31 g/L incurred at least one episode of over-anticoagulation while there was a total of 33 episodes of over-anticoagulation overall among those patients. The results of the statistical analysis using a Cox Regression model indicated that a normal albumin level was a protective factor against an episode of over-anticoagulation (Sig.=0.002; Exp(B)=0.950). These results are consistent with previous studies, suggesting that patients with a low albumin of less than 30 g/L are more sensitive to warfarin (Horton & Bushwick 1999; Roberts et al. 2003). Furthermore, results of the Poisson model revealed that patients with a serum albumin level within normal limits could expect that there would be no increase in the incidence rate ratio for episodes of over-anticoagulation (P>[z]=0.000; IRR=-0.941).

As over 50% of patients who recorded an albumin level less than 31 g/L incurred an episode of over-anticoagulation, it would appear that few doctors take serum albumin levels into consideration during the loading dose phase of warfarin therapy or are unaware that patients with an albumin level less than 31 g/L have an increased sensitivity to warfarin during this time (Roberts et al. 2003). The implications of this conclusion are important because the number of patients who had a decreased serum albumin level in

this study was considerable, suggesting that many episodes of over-anticoagulation may have been preventable had an altered dosage during the loading phase been considered.

5.9.10 Haemoglobin levels and episodes of over-anticoagulation

Although 97.6% of patients in this study had a Hb conducted prior to commencement of warfarin therapy, there were 26 patients whose Hb was recorded as less than 100 g/L. However, results of the statistical analysis using a Cox Regression model indicated that Hb, as a predictive covariate for an episode of over-anticoagulation, was not significant (Sig.=0.072). Conversely, when the Poisson model was applied to the data, results indicated that the level of Hb was significant (P>[z]=0.003; IRR=0.990) which suggests that a normal Hb level can expect to decrease the incidence rate ratio for an episode of over-anticoagulation, if all other variables in the model are kept constant.

Shireman et al. (2004) suggested that anaemia may expose patients to a higher risk of bleeding, although unknown factors such as cerebral vascular disease may have played a role in contributing to the increased risk and could not be ruled out. Because the findings of this study were varied and there is limited data available regarding the impact of low Hb levels in patients receiving warfarin therapy, further research would provide clarification of this issue.

5.9.11 The Hospital at Home Services and episodes of over-anticoagulation

Because a large proportion of patients who commenced on warfarin therapy at the study hospital were transferred through the Hospital at Home Services, it was important to determine whether this process was a protector for patients against episodes of over-anticoagulation. Results indicated that although as a predictive factor for an episode of over-anticoagulation the Hospital at Home Services was only marginally significant (Sig.=0.035), when data were applied to the Poisson model to estimate the incidence rate ratio for an episode of over-anticoagulation, results were significant (P>[z]=0.001; IRR=0.612). These results indicate that the incidence rate ratio could be expected to be reduced, while holding all other variables in the model constant.

Thus, these results indicate that for patients progressing through the Hospital at Home Services at the study hospital, this was beneficial in reducing the incidence of episodes of

over-anticoagulation, but was not significantly predictive of an episode of over-anticoagulation. This is important, because the implications of these findings are that patients who progress through the Hospital at Home Services will incur fewer episodes of over-anticoagulation, thereby creating a safer environment for patients during the first few days of warfarin therapy. It is after patients are discharged from the Hospital at Home Services that close management and frequent INR monitoring should continue for the first month especially, and this will be further discussed below.

5.9.12 Best predictive model for an episode of over-anticoagulation

While the findings of this study indicate that there were a very small proportion of doctors who reported that they used a scoring system to stratify the risk of bleeding, there were several doctors who indicated that they would use one if a reliable system were established. There have been several previous studies that have devised a scoring system to reduce the risk of bleeding complications during warfarin therapy, as mentioned above in this chapter (Beyth, Quinn & Landefeld 1998; Gage et al. 2006; Kuijer et al. 1999); however, it would appear that they are neither widely known or used. While it was not the intention of this study to establish a scoring system to reduce the risk of bleeding complications, it was important to attempt to clarify those covariates when added to a predictive model that could be utilised to estimate the number of episodes of over-anticoagulation as a means of prevention.

Using the Poisson model to estimate the best predictive model for the incidence rate ratio of episodes of over-anticoagulation, the covariates frequency of monitoring during the initial month of treatment and a decreased oral intake emerged as significant factors along with serum albumin levels and the Hospital at Home Services. All other previously significant covariates, when added to the model, were eliminated as the information they contained overlapped with each other. Careful analysis of predictive covariates for an episode of over-anticoagulation is essential in managing patients receiving warfarin. Therefore, further research that is able to establish a practical and simple scoring system that can predict or estimate the incidence rate ratios for an episode of over-anticoagulation would clearly be beneficial to doctors. The researcher acknowledges that the above predictive model is in the preliminary stage only, and the task to achieve such a tool is complex; however, future research that succeeded in developing a log equation that

doctors could apply in a practical manner, that is, add significant covariates to the equation as they arise, would be invaluable.

5.9.13 Conclusions regarding research question

In order to draw conclusions regarding the research question, the results of all five objectives of the study were addressed. In relation to Objective One, which was to assess the frequency of monitoring that occurred during the initial month of therapy, it was revealed that although the mean frequency was within the published guidelines, approximately 30% of patients had fewer than the recommended number of INR tests performed during that time. Furthermore, when a Cox Regression model was applied to evaluate whether the frequency of monitoring during the initial month of treatment was a significant factor for predicting episodes of over-anticoagulation, the results indicated that it was a very significant factor (Sig.=0.000). In addition, when the Poisson model was applied, results revealed that the incidence rate ratio was likely to increase by 1.08 times with infrequent monitoring during the initial month of treatment, if all other variables were held constant. While the frequency of monitoring during the initial month of treatment is one aspect of warfarin management only, these results reveal that it is a very significant factor in contributing to the prevention of episodes of over-anticoagulation.

In relation to Objective Two, which was to determine the number of episodes of over-anticoagulation during the initial month of therapy, the findings of the study revealed that overwhelmingly the majority of episodes of over-anticoagulation occurred during the initial month of therapy and became progressively fewer each month thereafter. The most common cause for an episode of over-anticoagulation was reported as medication interactions, followed by inappropriate dose adjustments and poor patient compliance. These results are significant in that they indicate that, first, the INR was unstable during the initial month of treatment and that subsequently the patient was exposed to an increased risk of bleeding. Second, while the cause/s of all episodes of over-anticoagulation were not known, the cause/s of many were known and potentially preventable with increased awareness by doctors and nurses of the impact of medication interactions and closer management with appropriate dose adjustments.

In relation to Objective Three, which was to determine the number of major bleeds during the initial month of therapy, all major bleeds except one occurred during the initial month

of therapy in this study, indicating again that, overall, patients were at a higher risk of adverse events during the initial month of therapy. While previous studies have shown that approximately 50% of bleeds occur while the INR is within or below the target range (Oake et al. 2007), Landefeld and Beyth (1993) found that the risk of a bleed was 10-fold higher during the initial month of treatment. Furthermore, the results in this study revealed that 52% of all bleeds occurred during the initial month of treatment. Despite this, Oake et al. (2007) found in a meta-analysis that improved INR control would reduce the likelihood of approximately 50% of all adverse events associated with oral anticoagulants. These results indicate that although approximately only half of the bleeds occurred when the INR was above the target range, close management and improved INR control have the potential to reduce the incidence of episodes of over-anticoagulation.

In relation to Objective Four, which was to assess the patient's understanding of warfarin therapy, general health and degree of compliance prior to episode of over-anticoagulation while receiving warfarin treatment, the findings of the study revealed that the level of general warfarin knowledge by patients was poor. According to previous studies (Arnsten, Gelfand & Singer 1997; Cheah & Martens 2003; McCormack et al. 1997; Lloyd & Rodgers 1994) this was likely to impact on the degree of compliance. This occurrence appears to be similar in this study where compliance was less than satisfactory on many occasions. These results were consistent with quantitative data obtained from the questionnaire completed by the doctors in this study who revealed that patients' general understanding of warfarin therapy and compliance was an issue that presented as a barrier to the management of warfarin therapy. These results are significant for two reasons. First, they indicate that patients are discharged home into the care of their GP with inadequate knowledge for managing their warfarin therapy during the time when they are at the greatest risk of incurring an adverse event. Second, the outcome of poor knowledge and compliance by many patients suggests that improvement is possible. Improved education can potentially improve compliance, which in turn can improve the management delivered by treating clinicians and the potential for prevention of episodes of over-anticoagulation and bleeding complications.

In relation to Objective Five, which was to assess current trends and concepts in medical management of patients receiving warfarin therapy in hospital and community setting, the findings of the study, based on the questionnaire completed by the doctors, indicate that overall they have concerns with oral anticoagulation in the elderly and the risk of

bleeding, medication interactions, instability of the INR and the level of knowledge and degree of compliance of patients receiving warfarin. The findings also revealed that a little over 50% of the doctors who completed the questionnaire reported that they could predict instability in the INR at least sometimes and the majority of doctors reported that they would investigate the cause of an INR>4.0. These results are significant in that they confirm that patient knowledge and compliance are low and that at least many episodes of over-anticoagulation are potentially preventable.

Finally, inferential statistical analysis of the covariates of interest indicate that low serum albumin, diarrhoea for at least two consecutive days, the presence of CCF, amiodarone, antibiotics, increasing age and the frequency of monitoring during the initial month of therapy were all significant predictors of episodes of over-anticoagulation. While the interaction between warfarin and many of these covariates has been discussed in previous studies, some extensively, these results remain important because they not only add to the bulk of knowledge, but they contribute to the concept that many episodes of over-anticoagulation are potentially preventable.

When all of the major findings of this study were examined, they clearly indicated that many of the episodes of over-anticoagulation were preventable as opposed to being unforeseeable. The concept of prevention of episodes of over-anticoagulation is not new and has been validated by several previous studies, which suggests that identification of risk factors, conscientious management and frequent monitoring rather than excluding high-risk patients from warfarin therapy might prevent many episodes of over-anticoagulation and subsequently reduce the risk of bleeding (Beyth, Quinn & Landefeld 1998; Ho & Brighton 2002; Merli 2002; Panneerselvam et al. 1998). The results of the above studies are similar to the concerns aired by doctors in this study who indicated that medication interactions were among the most commonly reported causes of instability of the INR. Additionally, many studies have reported the importance of patient education concerning warfarin therapy and INR management, in particular, the importance of knowledge of bleeding and vigilance for signs and symptoms of blood loss and when to report them to the doctor (Arnsten, Gelfand & Singer 1997; Bajorek et al. 2007; Cheah & Martens 2003; Ho & Brighton 2002).

In conclusion, it appears from the findings of this study and other studies mentioned above that at least some episodes of over-anticoagulation are potentially preventable as opposed to being unforeseeable. The results also indicate that rigorous and meticulous

management of the INR with increased frequency of monitoring especially during the initial month of treatment, and patient awareness of key aspects of warfarin therapy are the major means to preventing episodes of over-anticoagulation. Given the significance of these results, research to investigate the concept of prevention of episodes of over-anticoagulation further is warranted to conclusively clarify and quantify those key aspects of warfarin management that can best predict such events.

5.10 Implications for policy and practice

While there have been many studies that have investigated warfarin management and patients' knowledge and degree of compliance, Bungard et al. (2000) suggested that few have directly questioned doctors regarding their current medical management trends in warfarin therapy in the Australian community. This exploratory, descriptive survey is the first of its kind in Australia to provide multifaceted quantitative data pertaining to the frequency of INR monitoring, episodes of over-anticoagulation, bleeding events, current trends in medical management and patients' knowledge and degree of compliance in the hospital and community setting during the initial five months of treatment. Furthermore, for the first time in Australia, this study examines whether episodes of over-anticoagulation are potentially preventable. Results from a recent report released by the Australian Institute of Health and Welfare (2006) indicate that not only is Australia's population ageing, but that this will result in an increasing number of people with disabilities from diseases that are more common in older ages. AF is at present the most common arrhythmia treated by cardiologists and general practitioners and it is expected that the incidence of AF will continue to rise as the population ages (Ninio 2000). Moreover, it is highly unlikely that a new anticoagulant agent as effective as warfarin will be introduced in the near future and warfarin will thus remain the most widely available oral anticoagulant in Australia (Garcia et al. 2005). Therefore, this study is timely and its findings and recommended strategies will make a significant contribution to the healthcare literature.

The major finding of this study is that the initial month of warfarin therapy is a high-risk period, the results of all analyses showing that the majority of major bleeds occur during this time as well as the majority of episodes of over-anticoagulation. Therefore, this is the crucial period of time for the prevention of potential adverse events. Furthermore, the

findings revealed that patients being discharged home have poor knowledge of their warfarin treatment. Additionally, it appears from the findings of this study and other studies conducted in Australia (Bajorek et al. 2007; The Newcastle Anticoagulation Study Group 1998), that the day-to-day management of warfarin therapy has been defaulted to the GP almost exclusively. However, with the current critical shortage of GPs in Adelaide and the increased number of elderly patients being commenced on warfarin for the treatment of AF, it is clear that GPs should not be expected to deliver the effective and comprehensive warfarin management program that is urgently needed. Furthermore, it appears from the findings of this study and other studies (Bajorek et al. 2007; Peterson et al. 2002; The Newcastle Anticoagulation Study Group 1998), that there remain several areas of concern regarding the initiation and management of patients receiving warfarin.

First, it is clear that GPs need to play a more active role in the decision-making process concerning warfarin initiation and the suitability of the patient's ongoing treatment with specialists and cardiologists. There is also a need for consolidation and simplification of practical information and scoring systems for assessment of patients' risk factors for suitability of treatment and risk of episodes of over-anticoagulation and bleeding. A large proportion of doctors in this study did not inform patients as to the duration of therapy nor did they regularly reassess patients for their ongoing risk:benefit ratio of warfarin therapy. The researcher suggests that a wider dissemination of clinical trials information to GPs with clear and concise guidelines specifically related to the risk factors is required, especially for the elderly population, which has also been recommended in previous studies (Bajorek et al. 2007; Jackson, Peterson & Vial 2004; Peterson et al. 2002).

The researcher suggests that the introduction of an established tool/model that provides uniform guidelines and instils confidence in GPs in the decision-making processes of warfarin initiation and reversal of episodes of over-anticoagulation be made available to doctors, especially GPs in the community. The researcher also suggests that it include systematic documentation of the strict pathophysiology of stroke in the presence of AF. Additionally, more verbal interactive communication between specialists and cardiologists with hospital-based doctors and GPs to assist in the selection of suitable treatment for individual patients is required, which has also been suggested by Bajorek et al. (2007) and Peterson et al. (2002). The researcher further suggests that the knowledge of pharmacists in both the hospital setting and the community is utilised more efficiently with the promotion of educational programs for doctors and nurses. An evaluation of the

reasons why many GPs do not attend the practice incentive programs provided by the National Prescribing Service, including the design and delivery of such programs, would be of further value in the future. This in turn may lead to a better understanding by GPs of the risk:benefit ratio and an increase in the prescribing of warfarin for appropriate patients. One such educational intervention conducted in Tasmania, where GPs were sent guidelines on stroke risk stratification and antithrombotic drug use in AF followed by further educational sessions by pharmacists resulted in a significant increase in the use of warfarin in patients at high risk of stroke (Jackson, Peterson & Vial 2004). Pharmacists are ideally placed to provide such ongoing information and continued support to doctors and nurses, especially, community-based doctors and nurses.

Second, the researcher suggests that for patients to obtain the full benefits of warfarin therapy, all health care professionals involved in the care of patients receiving warfarin therapy must embrace the problem together. POC monitoring/management by those patients able and willing to do so would substantially reduce the burden carried by GPs in the community. It would help to augment patients' knowledge and awareness and encourage responsibility for their own health status. Bereznicki et al. (2006) suggests that accredited pharmacists are ideally placed to identify and deliver training to those patients willing and able for POC monitoring in the community. For those patients who do not qualify for POC monitoring, the establishment of community warfarin clinics would provide all patients, including those patients involved with POC monitoring, with a practical, comprehensive and uniform system for warfarin management. The clinics would provide practical ongoing information by specially trained nursing staff and pharmacists to encompass all topics that are essential for patients to be aware of, especially information that targets the main problem areas of management and those topics that concern patients most. That is, drug interactions, including OTC medications, dietary and alcohol intake, the importance of regular INR monitoring and the signs and symptoms of bleeding caused by warfarin and when to report them.

The researcher suggests that the information delivered to patients should be interactive and involve face-to-face discussions. Importantly, the information must be tailored to the individual's learning needs, especially to the elderly and illiterate patient's learning needs, and include patients' carers and family members when appropriate. Readily available information in the form of videos or printed material that is practical and can be used by the patient must be provided in a paced manner and there must be an opportunity

for verification of knowledge transfer. Finally, the information must be accessible on an ongoing basis so patients do not feel abandoned in their management of warfarin. Previous research also suggests that many patients experience difficulty in applying knowledge once discharged from the hospital (Bajorek et al. 2007; Cheah & Martens 2003). Therefore, access to ongoing current information is vital. Moreover, nurses and pharmacists would be able to conduct home visits for monitoring of medications, continuing education and re-evaluation of patients' understanding of warfarin as required. This strategy would be immensely valuable for those patients burdened by transport and/or mobility problems and ongoing illness.

Previous studies have identified that adverse drug events, particularly those regarding warfarin, are common and often preventable, especially among the elderly population post-discharge from hospital. This indicates that assessment of the patient's management in the home provides an invaluable opportunity to detect problems, educate and empower patients (Gurwitz et al. 2003; Stewart & Pearson 1999). Additionally, the transfer of patient information from hospital to community-based health professionals is essential to provide the seamless transition of care of patients on discharge, especially for those patients who incur multiple institutional transitions prior to being discharged home (Jackson et al. 2004). Peterson et al. (2006) made several recommendations to facilitate the quality of medicines between hospital and community. Some of these strategies included the national roll-out of a medication information sharing process between hospitals and community pharmacies, implementation of an automatic post-discharge home review in high-risk patients that would include education, medication review and INR monitoring, and the supply of a comprehensive medication information sheet for the patient/carer, GP and community pharmacist on discharge from hospital (Peterson et al. 2006). This researcher also believes agrees that such strategies would greatly enhance the patient's understanding of warfarin. This would thereby help them to detect problems in the acute period of high risk immediately post-discharge from hospital.

The above strategies have important implications for practice. First and most importantly, a major emphasis should be placed on the initial month of treatment when, as some previous studies and the findings of this study indicate, the patient is at the greatest risk of incurring an adverse event. Second, the strategies have the potential to streamline the management of patients and provide current and ongoing education at a central base

where patients could convene. For those patients unable to attend the community warfarin clinics due to physical or financial burdens, home visits would be made available.

The warfarin clinics would ideally be placed in the GP Plus Health Care Centres proposed by the Department of Health of the Government of South Australia. According to the government, the rationale is to make the GP Plus Centres the foundation of primary health care which would ease the pressures on emergency departments and health care personnel in hospitals. There is a plan by the government to build up to 10 centres across Adelaide and several more in country areas across the state, with two centres already built in Adelaide. Each centre will vary according to the needs of the local communities (Government of South Australia 2007b). Importantly, the clinics would alleviate the present-day time-consuming and costly process experienced by many GPs and hospital emergency departments while delivering ongoing comprehensive management programs that would include the above-mentioned strategies to those patients on warfarin therapy.

In order to evaluate the proposed strategies and interventions, a statewide warfarin database could be established. The establishment of such a database would have important implications for policy. It would mean that patients would be able to connect with the database to access their own personal records of INR results and dosages which would provide them with a complete record if travelling abroad, changing place of abode or having difficulty in maintaining stability of the INR for any reason. A database would also provide doctors with a comprehensive and accurate record of INR results and dosage patterns of their patients if admitted to hospital. As a final point, the database could be utilised as a reporting base for adverse warfarin events, which would assist in reducing such events and identifying problem areas.

5.11 Recommendations for future research

This study provides important information for the medical and nursing professions in Australia and opportunities for conducting large-scale studies to further standardise the initiation and management of patients receiving warfarin therapy.

A longitudinal study extended over five to ten years, conducted in the warfarin clinics suggested above, would allow for research to further explore and evaluate many of the strategies suggested and the concerns which could not be addressed in this study. Some of the concerns include the transition of patient information from hospital to community and

the increased frequency of monitoring, cost-effectiveness and outcomes after the initial month of therapy. The researcher acknowledges that the cause of many episodes of over-anticoagulation were unknown in this study due to inadequate information being available. It is not known whether, if this information were available, a cause would be identifiable or not. A longitudinal study conducted in the warfarin clinics would be able to provide more information, which may lead to the specific causes of such events, which would be invaluable in the future. Furthermore, given the significance of the findings of this study concerning the predictability and prevention of episodes of over-anticoagulation, further research is warranted to conclusively clarify and quantify those key aspects of warfarin management that can best predict such events.

Research of this magnitude has not previously been conducted in the community in the Australian setting. A longitudinal study involving patients receiving warfarin therapy in a clinic situation conducted over several years and involving a large sample would potentially allow for a new national policy to be formulated regarding the day-to-day management of patients receiving warfarin therapy. This would provide evidence-based practice in the Australian context that could be applied nationally.

Furthermore, it is the responsibility of all nurses, hospital-based and community-based, to be knowledgeable in the key elements of warfarin management especially since they are strategically placed in their role as the primary and often daily care givers of patients. It is the experience of the researcher that many hospital-based nurses currently do not involve themselves in the education of patients receiving warfarin because they believe that the doctors, pharmacists and/or home nurses attend to it. It is essential that all health care professionals are involved in the delivery of care and education of patients receiving warfarin. Thus, future research that examines the role of nurses in the management of patients receiving warfarin therapy in both the hospital setting and the community setting would be extremely beneficial in order to best utilise all resources available.

5.12 Strengths and limitations of study

As mentioned at the beginning of Chapter 5, the purpose of this study was to examine the process of management of patients receiving warfarin therapy through the hospital/community interface from initiation for a period of five months, or less if warfarin therapy was ceased prior to this time, and to provide a foundation for future

research in the clinical setting. While the generalisability of the results is limited by the use of a convenience sample, plus the inability of the study to determine cause-and-effect relationships between variables, the findings remain significant to practising doctors, nurses and pharmacists.

Randomised clinical trials include highly selective participants that are closely monitored for strict adherence to the study protocol and treatment environment, which can create the potential for artificiality in the translation of results to current patient populations (Hylek 2003). Hylek (2003) further suggests that multiple factors exist in the clinical setting that impact on the optimal monitoring and management of patients by health care providers and patients' adherence to prescribed medication regimes. The strength of this exploratory, descriptive survey lies in the inclusion of data collected across a broad range of patients and clinical indications to provide a true 'snapshot' of the complex phenomenon under study and capture the full and true nature of the process of management of patients receiving warfarin therapy as it occurs naturally in clinical practice. The data from this study will provide researchers with important baseline information when planning for future randomised clinical trials.

5.13 Conclusion

In the initial chapter of this thesis an introduction and background to the research and the research problem and the rationale for the research were presented. The research aims and objectives and the research question and a description of the methodology of the study were also presented. Finally, the definitions, key assumptions and an outline of the thesis were provided. Chapter Two provided a critical analysis of the literature relevant to the research question and the aims and objectives of this study.

A comprehensive explanation of the methodology utilised, including an account of the paradigm used and a description of the statistical procedures were presented in Chapter Three. Detailed descriptions of the sample size, data sought, data collection and the ethical issues encountered were also presented in that chapter. The results were detailed in Chapter Four, followed by an extensive discussion of the findings and the conclusions in Chapter Five. The implications for policy and practice, plus the strengths and limitations of the research followed, as were recommendations for future research.

The aim of the study was achieved, namely, to examine the process of management of patients receiving warfarin therapy through the hospital/community interface from initiation for a period of five months, or less if warfarin therapy was ceased prior to this time. Furthermore, all five objectives and the research question were explored and described. Whilst the researcher acknowledges, through the utilisation of a non-experimental study, that the ability to infer causal relationships between the variables under investigation was not possible, significant quantifiable data concerning the complex relationships between the variables was collected and documented. Additionally, the findings support already documented evidence that the level of education and subsequent compliance by patients is poor overall and that doctors remain concerned about this problem and the risk of bleeding complications, especially in the elderly population. Thus, the findings of this study contribute to the medical and nursing literature by highlighting the gaps in the management of patients receiving warfarin therapy and signify that the health care profession as a whole must embrace the management of patients receiving warfarin therapy to realise its full benefits.

In conclusion, warfarin remains the most widely available oral anticoagulant in Australia for the primary and secondary prevention of thromboembolic events. Thus, future research efforts must be recognised as vital in order to reduce the potential risks and complications, which can result in increased stress and anxiety associated with those patients incurring adverse effects of warfarin therapy and extended hospital stays with subsequent increased debts.