Chapter Four
Analysis of Data

4.1 Introduction

Chapter Three provided a justification for the research paradigm and the methodology used in this study. Detailed descriptions of the sample and sample size were presented, as were the instruments and data collection procedures.

This chapter first presents the justification for the data analysis techniques utilised in this study. The findings of the study are then presented. Descriptive statistics were used to provide the first stage of the results and a description and summary of those results is presented. Inferential statistics were used in the second stage to enable the researcher to answer the research question and thus make an objective decision regarding the outcomes of the study as presented in Chapter Five.

4.1.1 Data analysis techniques

Nominal data were collected to indicate characteristics and variables of interest about the patients which included gender; indication for warfarin; current medications; medical history; place of initiation of warfarin, that is, hospital or GP rooms; whether the GP received a discharge letter if initiated in the hospital; whether the patient attended the outpatient's haematology department; and whether the patient had received previous warfarin and if so, what the reason for that was. Additionally, data were collected as to whether the patient had an Hb performed near the end of the study period, what treatment was administered when an INR>4.0 occurred, whether a new dose of warfarin was administered at this time, whether the patient incurred a major bleed or not and whether an Hb was attended to or not when the INR>4.0.

Furthermore, nominal and ordinal data were collected to obtain factual information regarding the patient's understanding of warfarin, their general health and the degree of compliance prior to an episode of over-anticoagulation in the format of a constructed questionnaire. Lastly, nominal data were collected from hospital-based doctors and community doctors to obtain factual information regarding current trends and concepts in the management of patients receiving warfarin, also in the format of a constructed questionnaire.

Beanland et al. (1999) defines nominal data as that data which consists of observations that are named or classified into various mutually exclusive and collective categories. Ordinal data, while used to show relative rankings of objects or events, do not exhibit intervals between numbers on a scale that are necessarily equal or have an absolute zero (Beanland et al. 1999). Nominal and ordinal data were collected because although they allow the least amount of mathematical manipulation, it was considered necessary to categorise the sample and to make statements concerning the frequency of occurrence in each class.

Interval and ratio data were collected to show rankings of events and subjects on scales and included the patient's date of birth, date commenced on warfarin, pre-dose INR, Hb, platelets, serum albumin and weight. The patient's INR results, warfarin dosages and corresponding dates were also recorded. Burns and Grove (1995:257) define the interval-scale measurement as scales 'which have equal numerical distances between intervals of the scale'. Because these scales follow the rules for 'mutually exclusive categories, exhaustive categories and rank ordering and are assumed to be a continuum of values', the magnitude of the attribute can be specifically defined (Burns & Grove 1995:257) and thus more manipulation of data can occur (Beanland et al. 1999).

Ratio data meet all the rules of other forms of measurement with the addition of absolute zero points (Burns & Grove 1995), making such data the highest form of measurement (Beanland et al. 1999). Ratio data, in particular, were used because according to Beanland et al. (1999), this level of data allows all mathematical procedures to be performed on it. Additionally, interval and ratio data were considered appropriate for the design of the study to obtain quantifiable data on which to perform statistical analysis.

The patient data were documented on a 'Data Collection Form for Patients' by the researcher (Appendix 12), while data pertaining to patient's understanding of warfarin therapy, general health and the degree of compliance prior to an episode of over-anticoagulation were documented on the 'Initial Questionnaire for Patients' (Appendix 1) and the 'Subsequent Episode of Over-Anticoagulation Questionnaire for Patients' (Appendix 2) by the researcher. Data pertaining to the current trends and concepts in the management of patients receiving warfarin therapy in the hospital and community setting were documented on the 'Initiation of Warfarin Therapy Questionnaire for Doctors' (Appendix 3) by the researcher. These raw data were then entered into an Excel database, cleaned and organised for presentation and thereafter transferred to two statistical

packages, SPSS version 15.0 (SPSS Inc. Chicago) and Stata version 7.0 (Statacorp, Texas) for analysis.

The data were organised into frequency and percentage distributions, with confidence intervals established using CONFINT version 4.0. Measures of central tendency (mean, median and mode) were included to summarise the data. Tables and graphs were used to create visual representations and summaries for groups of cases. Quantile-by-Quantile plots demonstrated the presence or absence of outliers and normality of sampling distributions of the data for age, serum albumin, Hb and frequency of monitoring during the initial month of treatment. All other covariates, such as sex, antibiotics, paracetamol, amiodarone, CCF, diarrhoea, decreased oral intake and the Hospital at Home Services were dichotomous variables and because they are not normally distributed (Garson 2007), were not tested. The Shapiro-Wilks test was applied to formally test for normality of the data prior to application of the inferential statistics. The data were also screened for skewness and kurtosis of the distributions. Survival analysis using the proportional hazard regression model (Cox Regression Model) and the Poisson distribution were used to model for analysis of time to an event and the probability of occurrence of events in time, respectively.

4.2 Descriptive statistics

4.2.1 Summary of data

The sample consisted of 294 men and women aged 18 years and above and of all cultural backgrounds who were admitted to the study hospital, and all consecutive patients attending the participating GPs' rooms or seeing the GP initially after being commenced on warfarin therapy elsewhere and alerted to the researcher between September 2005 and December 2006. All patients met the inclusion criteria previously described in Chapter Three. Inclusion criteria included all patients diagnosed with AF, DVT/PE, basilar artery thrombosis, venous sinus thrombosis, portal vein thrombosis, ventricular thrombosis, vertebral artery thrombosis, cerebellar occipital infarct and eye thrombosis and commenced on warfarin therapy. Those patients commenced on warfarin therapy for the prophylaxis of thromboembolism post-plantar fusion, post-myocardial infarct or post-prosthetic heart valve replacements were also included in the study.

Of the 294 patients 73 were interviewed using the 'Initial Questionnaire for Patients' after they had incurred a single episode of over-anticoagulation. A further 12 patients were interviewed using the 'Subsequent Episode of Over-anticoagulation Questionnaire for Patients' after they had incurred subsequent episodes of over-anticoagulation. Finally, ninety-nine GPs and forty-seven hospital-based doctors completed the 'Initiation of Warfarin Therapy Questionnaire for Doctors'.

4.2.2 Demographic characteristics of patients

Table 4.1: Place of warfarin initiation (n=294)

Place of warfarin initiation	Patients	%
Hospital	275	93.5
GP rooms	19	6.5
Total	294	100.0

Source: Analysis of study data using Excel

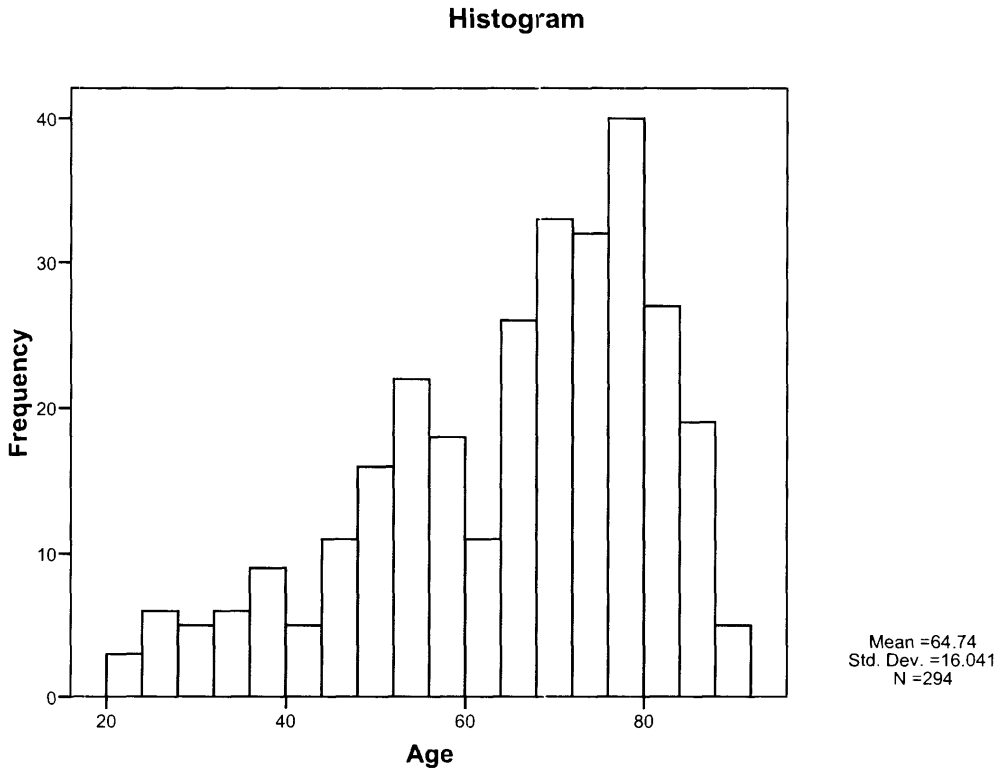
Table 4.1 shows that the vast majority of patients were initiated on warfarin therapy in the hospital setting, with only a very small number of patients being initiated on warfarin therapy in GP rooms.

Table 4.2: Gender of patients (n=294)

Gender	Patients	%
Female	113	38.4
Male	181	61.6
Total	294	100.0

Source: Analysis of study data using Excel

Table 4.2 shows that almost two-thirds of the patients participating in the study were male, while approximately one-third were female.



Graph 4.1: Age of patients

Source: Analysis of study data using SPSS version 15.0

Table 4.3: Age of patients (n=294)

Mean	64.7
Median	69.0
Mode	73.0*
Standard Deviation	16.0
Maximum	91.0
Minimum	20.0

*Multiple modes exist. The smallest value is shown.

Source: Analysis of study data using SPSS version 15.0

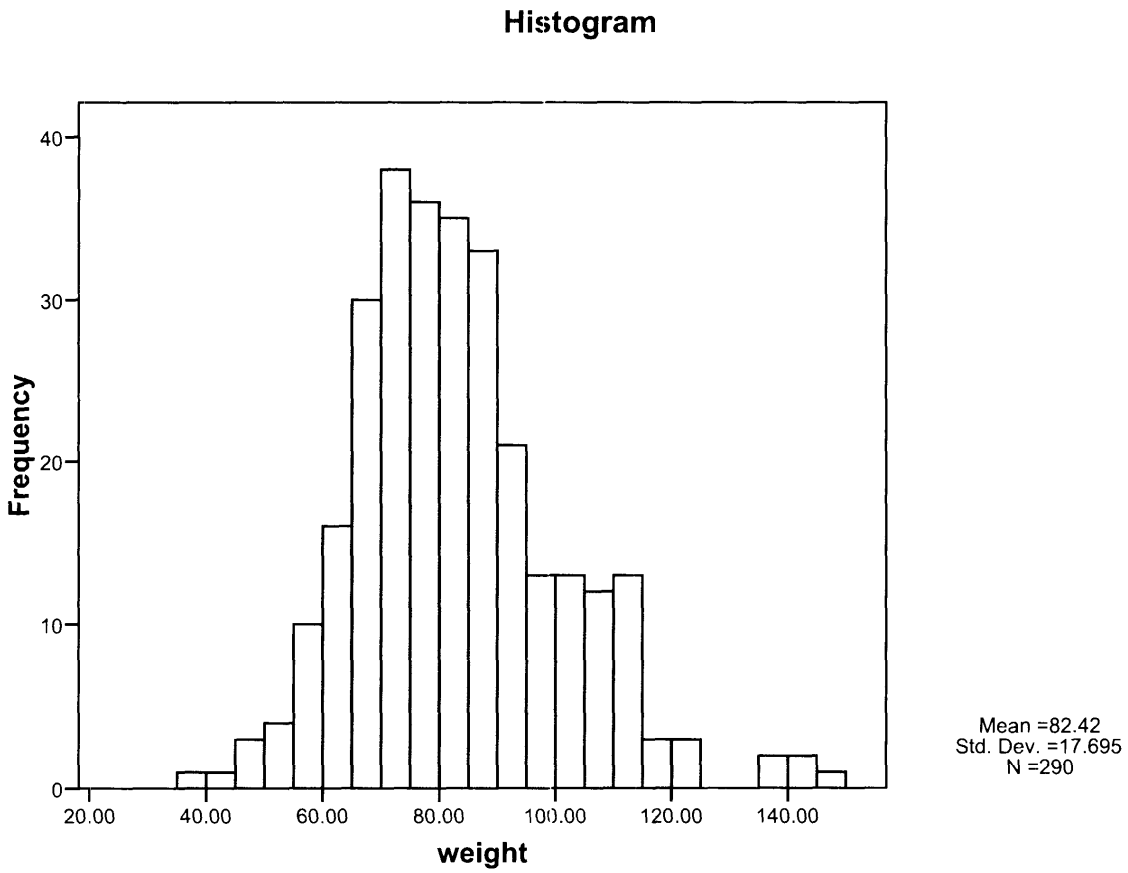
Graph 4.1 shows that the majority of patients who were commenced on warfarin were in the 70-80 years of age category, thus causing a negatively skewed distribution.

Table 4.4: Weight of patients (kilograms) (n=291)

Mean	82.4
Median	80.3
Mode	85.0*
Standard Deviation	17.6
Maximum	146.0
Minimum	35.5

*Multiple modes exist. The smallest value is shown.

Source: Analysis of study data using SPSS version 15.0



Graph 4.2: Weight of patients

Source: Analysis of study data using SPSS version 15.0

Graph 4.2 shows that there was a relatively large proportion of patients whose weight was above 90 kilograms.

Table 4.5: Indication for warfarin (n=294)

Diagnosis	Patients	%
Atrial fibrillation	145	49.3
Deep venous thrombosis/Pulmonary embolis	114	38.8
Post myocardial infarct	5	1.7
Other	30	10.2
Total	294	100.0

Source: Analysis of study data using Excel and CONFINT version 4.0

Of the 294 patients participating in the study, almost half were commenced on warfarin for the treatment of atrial fibrillation (49.3%. 95% CI 43.4-55.1) while more than a third were commenced for the treatment of DVT/PE (38.7%, 95% CI 33.1-44.6). The 30 (10.2%) patients categorised under 'other' were commenced for prophylaxis of thrombo-embolism post-prosthetic heart valve replacement, for the treatment of basilar artery thrombosis, venous sinus thrombosis, portal vein thrombosis, ventricular thrombosis, vertebral artery thrombosis, cerebellar occipital infarct, eye thrombosis and for the prophylaxis of thromboembolism post-plantar fusion.

Table 4.6: Proportion of patients receiving warfarin previously (n=294)

	Patients	%
Yes	47	16.0
No	247	84.0
Total	294	100.0

Source: Analysis of study data using Excel

Of those patients who had received warfarin therapy prior to this study, 23 (48.9%) had received warfarin for the treatment of DVT/PE, 12 (25.5%) had received warfarin for the treatment of atrial fibrillation, 1 (2.1%) had been commenced on warfarin post-infarct for a period of time and the remaining 11 (23.5%) patients were either not sure of the reason or the warfarin was prescribed for another reason not already mentioned.

Table 4.7: Discharge letters (n=275)

	Discharge letters	%
Yes	223	81.1
No	29	10.5
Uncertain	23	8.4
Total	275	100.0

Source: Analysis of study data using Excel

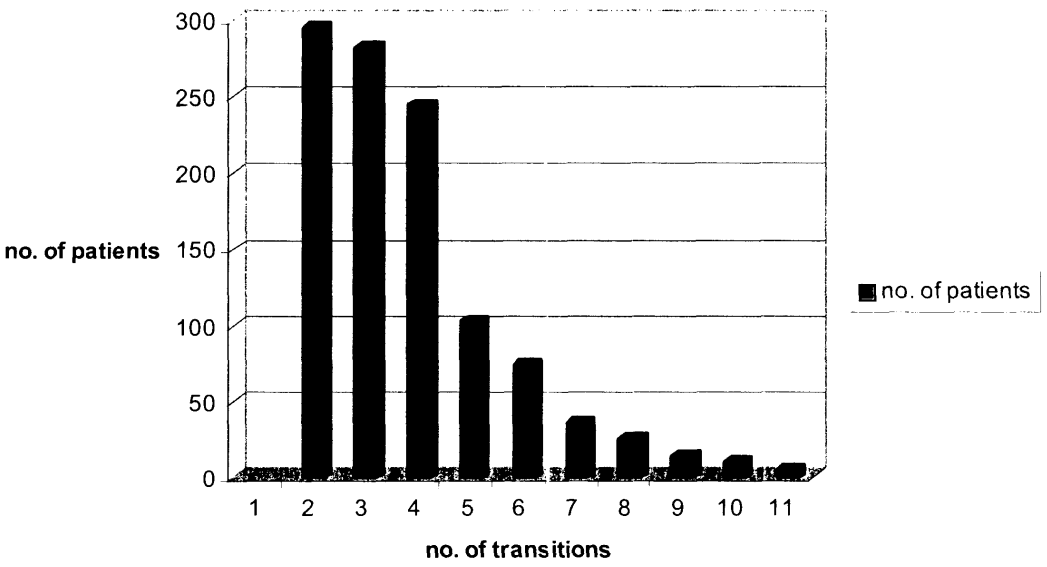
Several studies have reported that patients being discharged home from hospital are at a greater risk of incurring an adverse event through medication error, confusion associated with following the correct instructions and poor compliance (Anderson, Divers & von Hennigs 2005; Forster et al. 2003; Jackson et al. 2004; Stewart & Pearson 1999). If discharge letters containing adequate information concerning the patient's treatment / medications are not written or fail to reach the treating doctor in a timely manner, management of that patient may be compromised.

Table 4.7 shows that a large proportion of discharge letters were written and a copy placed in the patient's medical records. As it was not possible to check with all GPs or other health institutions as to whether the discharge letters were mailed in a timely manner, that is, on the day the patient was discharged from hospital, it was not known whether all GPs received the discharge letters to be of benefit. Furthermore, it was not known whether the letters were mailed to the correct GP or address or whether the patient continued to see the same GP on discharge from the hospital. Additionally, the discharge letters did not provide a complete record of the patient's INR results and warfarin dosages while in hospital. However, in an email communication on 8 March 2007, the Clinical Nurse Manager of the Hospital at Home Services and Flinders Liaison Service of the study hospital, reported that if the patient progressed through the Hospital at Home Services, a complete record of the patient's INR results and dosages were sent to the respective GP or institution on the patient's discharge (B. Farrelly 2007, pers. comm., 8 March). Again, it was not known whether this was accomplished in a timely manner to be of benefit or not.

Table 4.8: Patient transition periods (n=294)

Place of transition	1st transition (%)	2nd transition (%)	3rd transition (%)	4th transition (%)	5th transition (%)
Study hospital	87.0	1.3	14.3	44.7	9.4
Hospital at Home	1.1	74.4	1.7	12.6	12.2
GP rooms	6.5	19.5	75.8	30.1	70.2
Institute other than study hospital	5.4	3.8	2.1	10.7	4.1
OPD	0	0.6	6.1	1.9	4.1

Source: Analysis of study data using Excel



Graph 4.3: Patient transitions during five-month study period

Source: Analysis of study data using Excel

Table 4.8 shows that the majority of patients were commenced on warfarin therapy in the hospital setting, that is, either in the study hospital or an institution other than the study hospital initially, then transferred to the Hospital at Home Services before being discharged into the care of the GP. However, there was a considerable proportion of patients who were re-admitted to the study hospital at a later date before being again

discharged to the GP. As shown in Graph 4.3, a steady proportion of patients experienced many transitions back and forth through the study hospital, the Hospital at Home Services, their GP or an institution other than the study hospital. Table 4.8 also shows that only a small proportion of patients were transferred through the OPD for appointments.

Table 4.9: Concomitant medications taken by patients (n=294)

Medications	Patients	%
Aspirin	85	28.9
Paracetamol	61	20.7
Antibiotics	52	17.7
Amiodarone	38	12.9
Clopidogrel	23	7.8
SSRI	16	5.4
NSAIDS	7	2.4
Cox II	3	1.0
Aspirin/Dipyridamole	2	0.6

Source: Analysis of study data using Excel and CONFINT version 4.0

Several patients were prescribed more than one of the above listed medications at the same time. Table 4.9 shows that the most commonly prescribed concomitant medication that was included in the study was aspirin (28.9%, 95% CI 23.7-34.4), indicating that almost one third of patients received aspirin while receiving warfarin therapy. The second most common medication prescribed was paracetamol (20.7%, 95% CI 16.2-25.8).

Table 4.10: Patient co-morbidities (n=294)

Co-morbidities	Patients	%
HT	138	46.9
IHD	110	37.4
CCF	55	18.7
Diabetes	54	18.4
TIA	29	9.8
Malignancy	27	9.1
COPD	27	9.1
Embolic CVA	24	8.1
CRF	22	7.4
GIT bleed/ulcer	15	5.1
PVD	12	4.0
Liver disease	6	2.0
Platelet dysfunction	5	1.7
CVA haemorrhage	2	0.7
Coagulation defect	1	0.3

Source: Analysis of study data using Excel

The study findings revealed that the mean number of co-morbidities any one patient had a history of was 1.8, the median was 2.0 and the standard deviation was 1.6. The maximum number of co-morbidities any one patient had a history of was seven while the minimum was nil. Table 4.10 shows that almost half of the patients included in the study had a history of hypertension while over one third had a history of ischaemic heart disease (IHD). Additionally, a considerable number of patients had a history of congestive cardiac failure (CCF) and/or diabetes.

Table 4.11: Pre-dose INR results (n=268)

Mean	1.1
Median	1.0
Standard Deviation	0.1
Maximum	1.5
Minimum	0.8

Source: Analysis of study data using Excel and CONFINT version 4.0

Two hundred and sixty-eight patients (91.1%, 95% CI 87.3-94.1) had an INR recorded prior to commencing warfarin therapy. Of those INR results reported, 30 were outside the normal range of 1.0-1.3 as defined by Southpath Laboratories, 27 were less than 1.0 and 3 were greater than 1.3.

Of the three patients whose INR>1.3, patients # 1 and # 2 both had an INR=1.4 and were post-mitral valve replacement and aortic valve replacement respectively. Patient # 3, whose INR=1.5, was diagnosed with a large thrombus of the portal vein and lungs and subsequently commenced on warfarin therapy.

Table 4.12: Pre-dose haemoglobin (Hb) results (g/L) (n=287)

Mean	133.0
Median	136.0
Mode	136.0
Standard Deviation	21.7
Maximum	181.0
Minimum	77.0

Source: Analysis of study data using SPSS version 15.0 and CONFINT version 4.0

The proportion of patients with a pre-dose Hb was 287 (97.6%, 95% CI 95.1-99.0). Of the 88 results recorded outside of the normal range of 115-160 g/L as defined by the OASIS Database, 64 were less than 115 g/L and 24 were greater than 160 g/L.

Of the 26 patients whose Hb were recorded as less than 100 g/L, 20 were post-cardiothoracic surgery and three were diagnosed with a DVT/PE, of whom one had been discharged home four days earlier post-delivery of a baby. Of the remaining three patients, patient # 1 was diagnosed with a portal vein thrombosis post-hysterectomy and subsequently commenced on warfarin, patient # 2 was post-general surgery and developed a DVT, and patient # 3 was diagnosed with severe metabolic acidosis and coagulopathy secondary to metformin and diamicron and found to be in AF. This patient also had a serum albumin recorded at 29 g/L.

Table 4.13: Pre-dose platelet (x 10^9/L) count (n=286)

Mean	269.4
Median	254.5
Standard Deviation	95.1
Maximum	757.0
Minimum	106.0

Source: Analysis of study data using Excel and CONFINT version 4.0

Two hundred and eighty-six (97.2%, 95% CI 94.7-98.8) patients had a recorded pre dose platelet count. There were 28 results recorded outside of the normal range of 150-450 x 10^9/L as defined by Southpath Laboratories, with 15 of those results recorded as less than 150 x 10^9/L and 13 greater than 450 x 10^9/L.

Table 4.14: Pre-dose albumin (g/L) (n=278)

Mean	37.8
Median	38.0
Mode	40.0
Standard Deviation	5.5
Maximum	51.0
Minimum	17.0

Source: Analysis of study data using SPSS version 15.0 and CONFINT version 4.0

Two hundred and seventy-eight patients (94.5%, 95% CI 91.3-96.8) had a recorded pre-dose albumin level. There were 60 results recorded outside the normal range of 31-44 g/L as defined by Southpath Laboratories, with 31 recorded below 31 g/L and 29 above 44 g/L.

Of the 31 patients who recorded an albumin level below 31 g/L, 17 (55%) incurred at least one episode of over-anticoagulation, while there were 33 episodes of over-anticoagulation in total. However, one patient, who incurred seven episodes of over-anticoagulation during the study period, was believed to be self-dosing to deliberately incur an episode of over-anticoagulation. The patient's treating doctors were suspicious that the patient was non-compliant with the warfarin and was intentionally overdosing himself/herself in order to use medical problems as a means of legal defence in a criminal case.

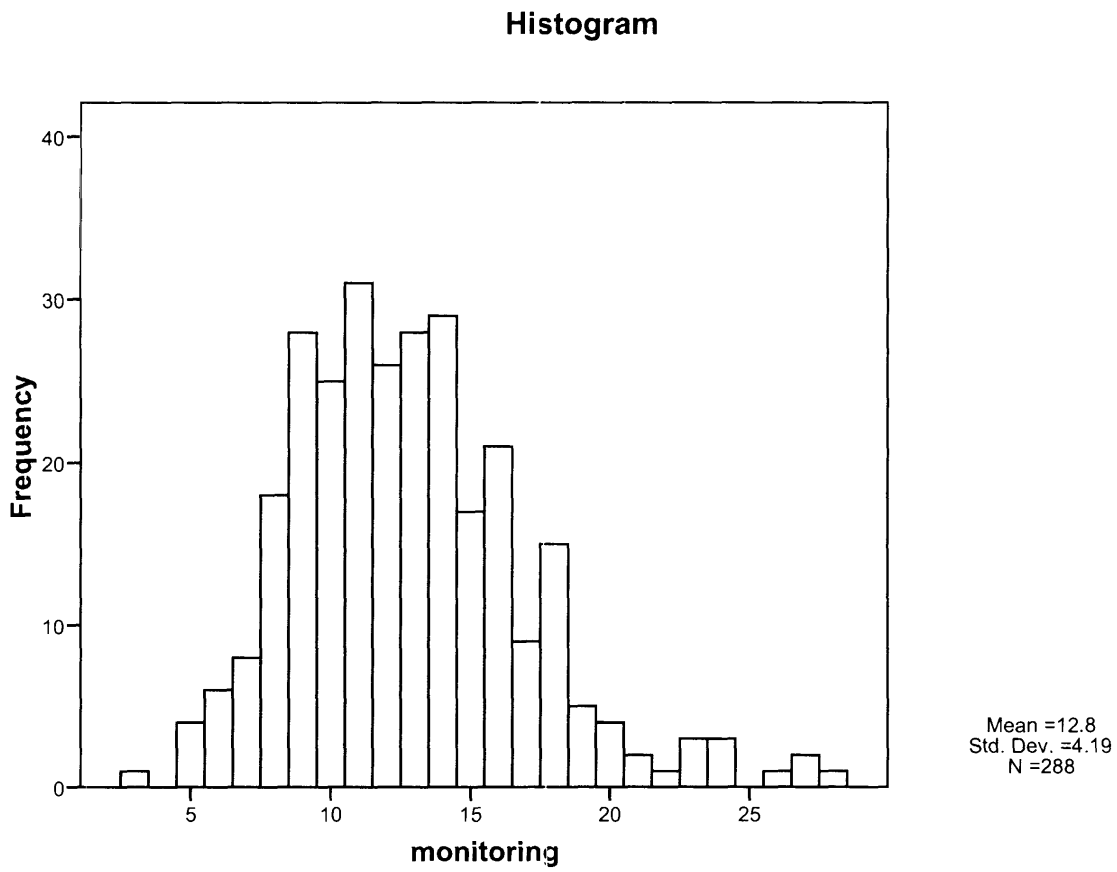
4.2.3 Objective 1: Determining frequency of INR monitoring during initial five months of warfarin therapy in both hospital and community setting

To achieve this objective this section will first present the data pertaining to the frequency of INR monitoring during the initial month (30 days) of warfarin therapy. After this, the data pertaining to the frequency of monitoring between months two to five will be presented.

Table 4.15: Frequency of INR monitoring during the initial month (30 days) of warfarin therapy (n=288)

Mean	12.8
Median	12.0
Mode	11.0
Standard Deviation	4.1
Maximum	28.0
Minimum	3.0

Source: Analysis of study data using SPSS version 15.0



Graph 4.4: Frequency of monitoring during initial 30 days of warfarin therapy (n=288)

Source: Analysis of study data using SPSS version 15.0

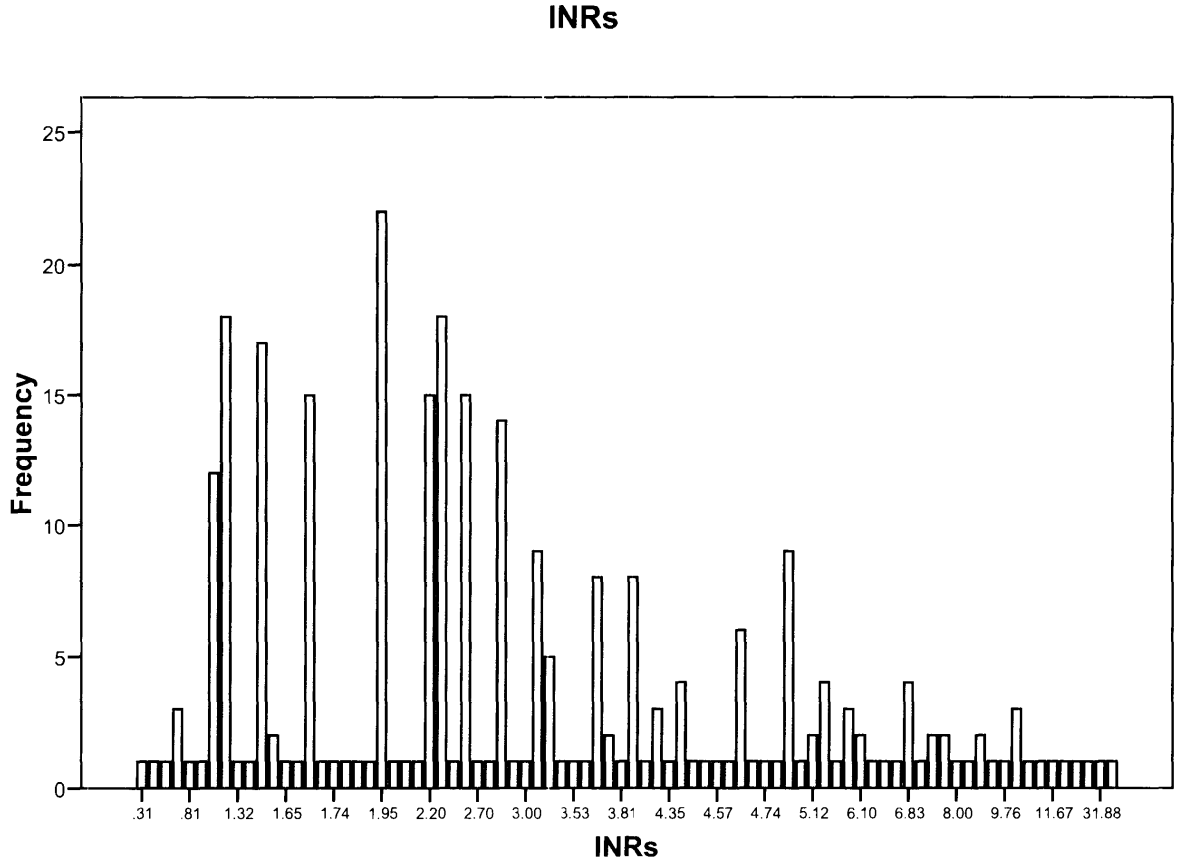
Graph 4.4 shows that the majority of INR tests were conducted between eight and 16 times per month.

Six patients had their warfarin ceased prior to the initial month and thus these patients were omitted from the analysis. The one patient who had three INR results recorded for the initial month was commenced in the GP's surgery and according to the GP's medical notes, failed to present for regular INR monitoring. There was also only one patient who had 28 INR tests for the initial month. This patient was post-cardiovascular surgery and was discharged from the hospital into the care of the GP.

The mean number of INR tests conducted among the 80 patients who completed an initial month of treatment and incurred an initial episode of over-anticoagulation during that time was 14.7 times, compared with a mean of 12.8 INR tests for the 288 patients overall

as shown in Table 4.15. The mean number of INR tests conducted for those 13 patients who incurred more than one episode of over-anticoagulation during the initial month of treatment was 16.2 times.

Although the mean number of INR tests conducted for the initial month was 12.8, there were 90 (31.2%) patients who had fewer than 11 INR tests conducted.



Graph 4.5: Frequency of INR monitoring per month during months 2-5 for all patients

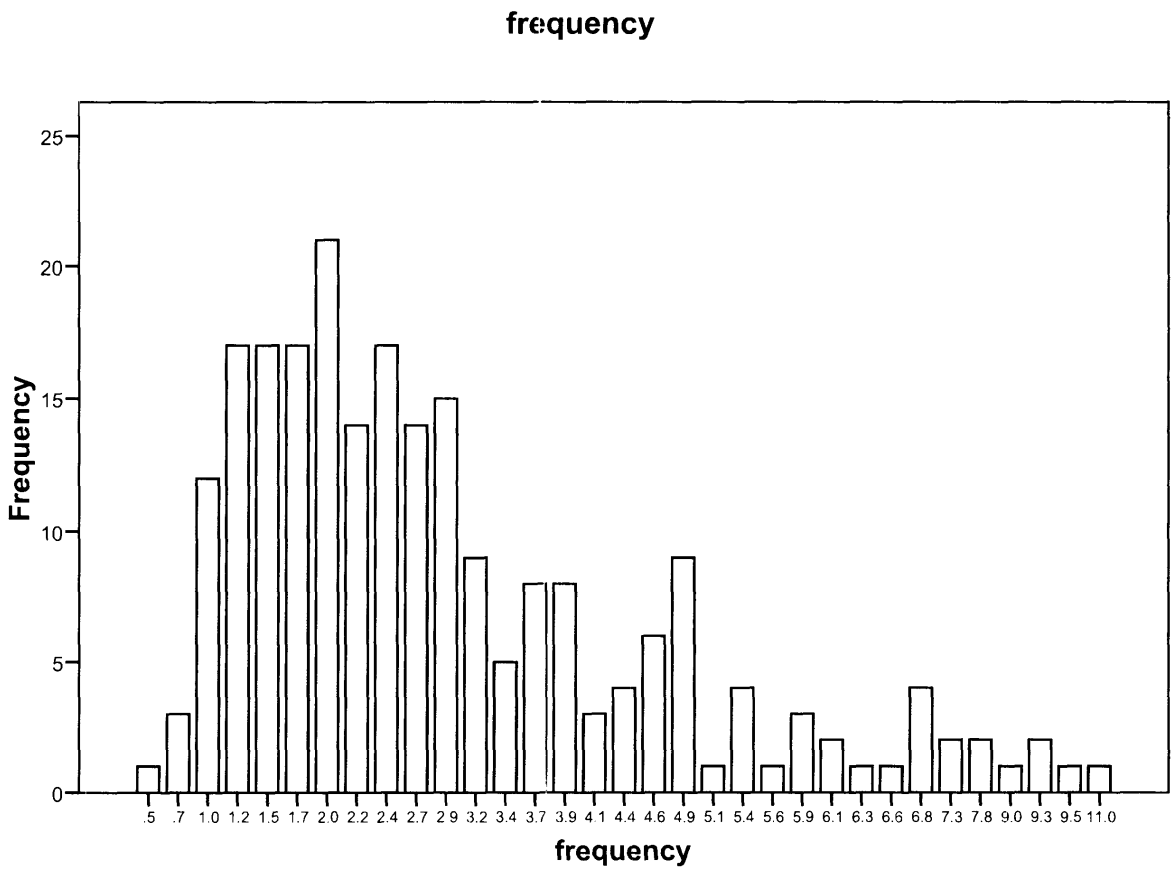
Source: Analysis of study data using SPSS version 15.0

Table 4.16: Frequency of INR monitoring per month between months 2-5 for all patients (n=285)

Mean	3.5
Median	2.6
Mode	1.9
Standard Deviation	3.7
Maximum	32.7
Minimum	0.31

Source: Analysis of study data using SPSS version 15.0

Graph 4.5 and Table 4.16 show that approximately once a fortnight was the most common number of times for an INR to be conducted between months two and five of warfarin therapy, with an overall average of 3.5 INR tests conducted per month. Not all patients received warfarin therapy for the duration of the study period, thus the maximum number of INR tests conducted for months two to five appears high. There were 56 patients who received warfarin therapy for less than 153 days, with six of those patients receiving warfarin for less than one month. Four patients had their warfarin ceased shortly after the initial month of treatment. These patients had intensive INR monitoring before having their warfarin therapy ceased.



Graph 4.6: Frequency of INR monitoring per month during months 2-5 for patients receiving warfarin for 153 days (n=225)

Source: Analysis of study data using SPSS version 15.0

Table 4.17: Frequency of INR monitoring per month during months 2-5 for patients receiving warfarin for 153 days (n=225)

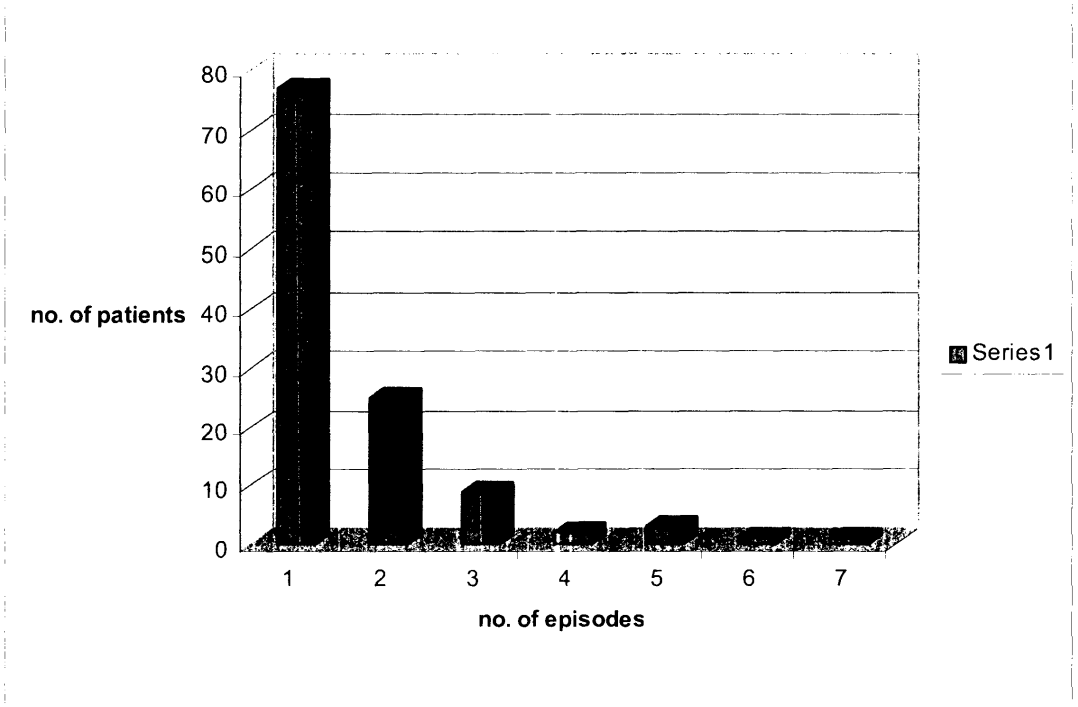
Mean	2.9
Median	2.4
Mode	2.0
Standard deviation	1.8
Minimum	0.5
Maximum	11.0

Source: Analysis of study data using SPSS version 15.0

Graph 4.6 and Table 4.17 show that for those patients who received warfarin therapy for 153 days, the average number of INR tests conducted per month between months two to five was 2.9.

4.2.4 Objective 2: Determining number of episodes of over-anticoagulation during initial five months of warfarin therapy, specifically in first month compared with subsequent months

There were 190 single episodes of over-anticoagulation among 294 patients during the study period. A single episode of over-anticoagulation was defined as an INR>4.0 occurring which was followed by two consecutive INR<4.0 within two weeks before the next INR>4.0 occurred. There were 117 patients who incurred at least one episode of over-anticoagulation and 177 patients who did not incur any episodes of over-anticoagulation during the study period. As shown below in Graph 4.7, of the 117 patients who incurred at least one episode of over-anticoagulation, 77 incurred one single episode, 25 incurred two episodes, 9 incurred three episodes, 2 incurred four episodes, 3 incurred five episodes and 1 incurred six episodes of over-anticoagulation. The maximum number of episodes of over-anticoagulation incurred by a single patient was seven. However, the patient's treating doctors were suspicious that, in addition to the occurrence of a drug interaction with an SSRI, the patient was extremely non-compliant and was intentionally overdosing him/herself in order to use his/her medical problems as a legal defence in a criminal case.



Graph 4.7: Number of patients who incurred episodes of over-anticoagulation

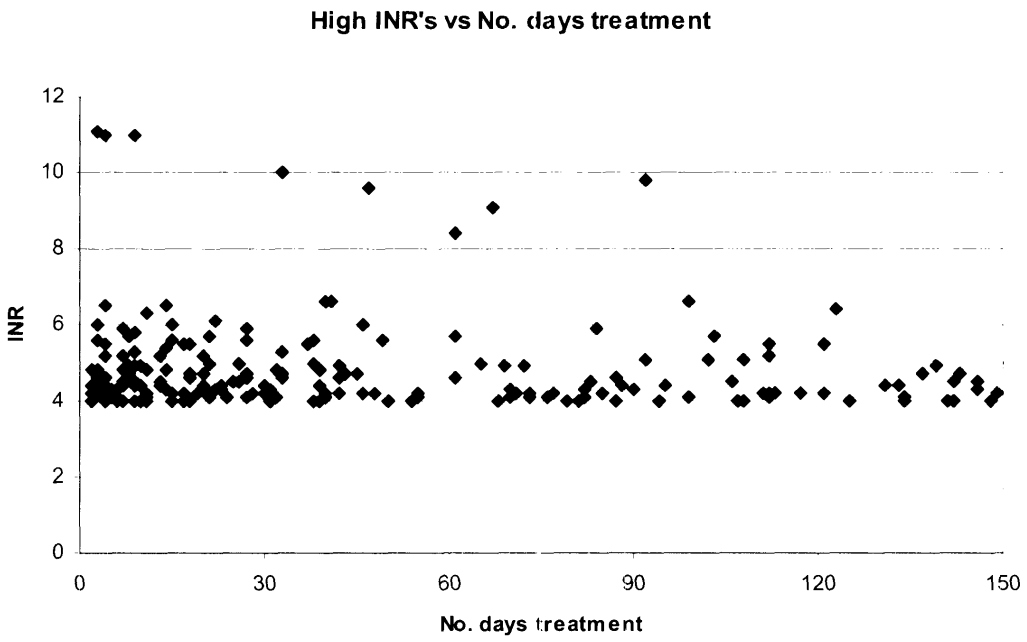
Source: Analysis of study data using Excel

Table 4.18: Number of patients who incurred at least one episode of over-anticoagulation during initial month of warfarin therapy (n=294)

INR	Patients	%
>4.0	82	27.9
≤4.0	212	72.1
Total	294	100.0

Source: Analysis of study data using Excel and CONFINT version 4.0

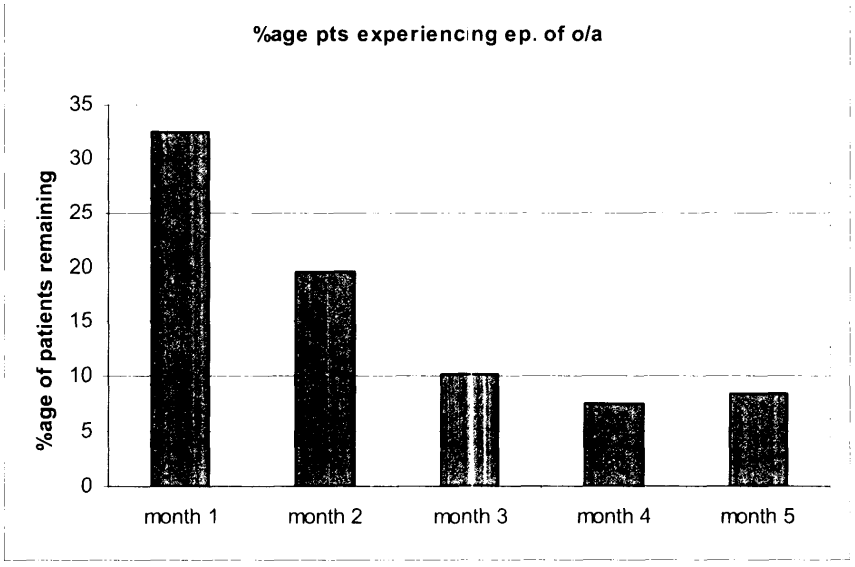
Just under one third of patients (27.9%, 95% CI 22.8-33.3) incurred at least one single episode of over-anticoagulation during the initial month of treatment while 88 patients (29.9%, 95% CI 24.7-35.5) incurred an INR≥4.0 during the initial month of treatment. Of the 117 patients who incurred at least one episode of over-anticoagulation during the course of the study, 82 (70.0%) patients had their one episode during the initial month of treatment.



Graph 4.8: Spread of INR levels ≥4.0 during the five-month study period

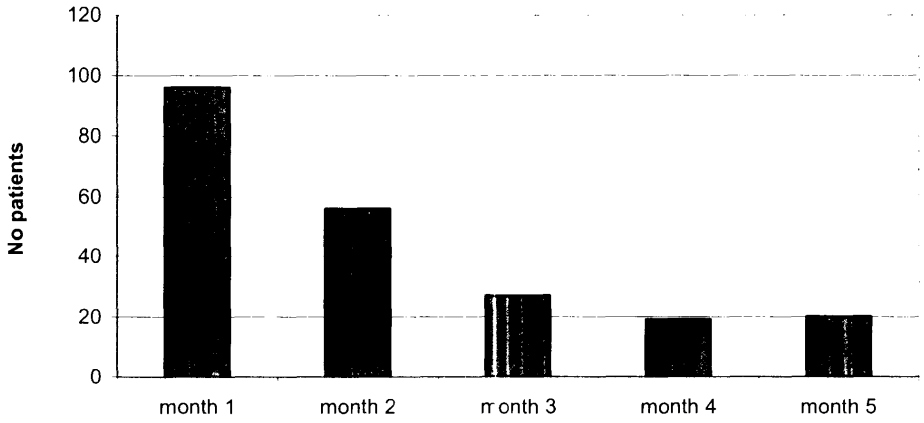
Source: Analysis of study data using Excel

Graph 4.8 clearly shows the clustering of INR results ≥4.0 shortly after the initiation of warfarin therapy during the initial month of treatment and the much less dense high INR results thereafter. The graph also indicates that the majority of high INR results fell between 4.0 and 6.0, with 11.1 recorded as the highest result, in the initial month of therapy.



Graph 4.9: Percentage of patients who experienced over-anticoagulation during first five months of treatment

Source: Analysis of study data using Excel



Graph 4.10: Monthly frequency of over-anticoagulation during first five months of treatment

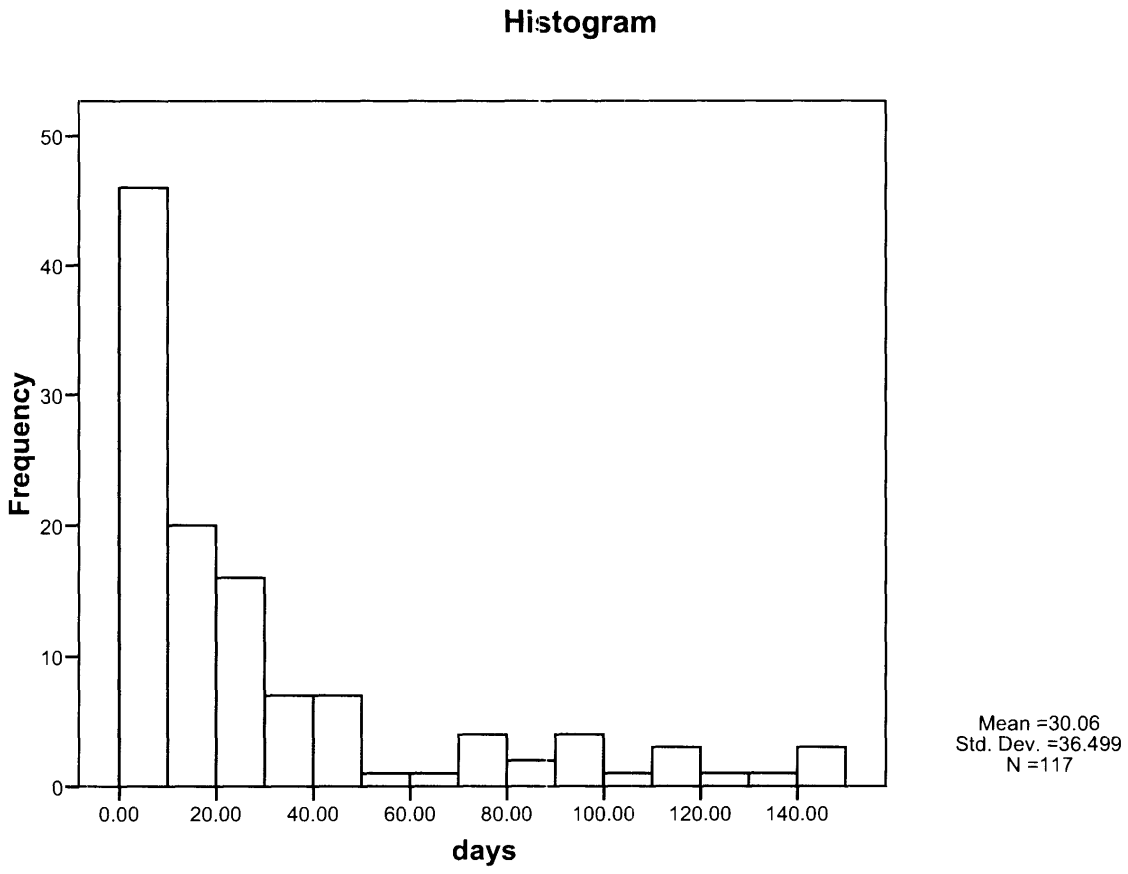
Source: Analysis of study data using Excel

Graphs 4.9 and 4.10 include the data for those patients whose INR results were equal to and greater than 4.0. Both graphs show clearly the extreme front-loading of episodes of over-anticoagulation during the initial month of warfarin therapy and the substantial decline in the subsequent months of treatment.

Table 4.19: Number of days after initiation of warfarin therapy that initial episode of over-anticoagulation occurred (n=117)

Mean	30.6
Median	14.0
Standard Deviation	36.4
Maximum	146.0
Minimum	2.0

Source: Analysis of study data using Excel and CONFINT version 4.0



Graph 4.11: Occurrence of initial episode of over-anticoagulation

Source: Analysis of study data using SPSS version 15.0

Graph 4.11 and Table 4.19 show clearly that while the majority of initial episodes of over-anticoagulation occurred during the first month of therapy, the bulk of these episodes occurred during the first and second weeks of therapy.

One hundred and seventeen patients (39.8%, 95% CI 34.1-45.6) incurred an initial episode of over-anticoagulation during the five-month study period. There were 27.9% of patients who incurred an initial episode of over-anticoagulation during the first month (first 30 days) of treatment, indicating that overwhelmingly the majority of initial episodes of over-anticoagulation occurred during the first month of treatment and that such episodes became progressively less frequent each month thereafter.

Table 4.20: INR results of initial episode of over-anticoagulation (n=117)

Mean	5.1
Median	4.7
Standard Deviation	1.3
Maximum	11.1
Minimum	4.1

Source: Analysis of study data using Excel

Table 4.20 indicates that the highest INR recorded was 11.1. There were four patients whose INR measurements were ≥11.0. No patient whose INR≥11.0 incurred a major bleed at the time of the elevated INR; however, patient # 1 experienced a psoas bleed/haematoma intramuscularly eleven days after the INR=11.1, when the INR was then 3.4. Subsequently, the patient was transfused with three units of blood. The cause of the INR=11.1 was most likely the patient's multi-system failure, profuse diarrhoea and the administration, some days previously and during the time of the elevated INR, of antibiotics known to increase the INR (azithromycin, gentamycin, flucloxacillin, penicillin and augmentin DF). Additionally, the patient had received three doses of warfarin, with the INR being measured once only during that time.

Patient # 2 was an 81year old female, whose INR>11.0 was likely to be attributed to overdosing. She received initial doses of 7 mg, 10 mg, 10 mg and 5 mg loading doses of warfarin, with only one INR taken the day after the initial 7 mg was given. The INR>11.0 on the next INR test, which was attended to on the fifth day of therapy.

Patient # 3 appeared to be confused as to dosage and management of the warfarin and hence the cause was most likely excessive dosage self-administered by the patient for an unknown period of time prior, resulting in an INR>11.0. The patient required re-admission to the study hospital and the administration of two units of FFP and vitamin K.

According to the patient's GP, the patient was prescribed 5 mg daily while it was thought the patient took up to 13 mg daily.

Finally, the INR>11.0 for patient # 4 was most likely due to a substantial increase in alcohol intake, by his/her own admission, during the two days prior to the INR being taken.

Although the highest INR recorded in the study was >12.0, it occurred 12 days after the five-month (153 days) study period and thus was not included in the final analysis. This was the patient's initial episode of over-anticoagulation. On this occasion the patient had suffered a bout of cold/flu-like symptoms and was feeling unwell for several days. He/she had also experienced painful gout in the leg and foot. The patient's oral intake was significantly decreased for four days prior to the INR>12.0 and he/she had been given colchicine for the gout, which gave the patient acute diarrhoea for the following two days, and subsequently he/she became dehydrated. The patient was also taking indocid 25 mg three times per day and two panadeine-forte every four hours for pain. Although the patient did not have a major bleed, he/she was readmitted to hospital during this time for treatment of over-anticoagulation and gout and suffered acute renal failure. Therefore, all of the abovementioned patients' INR results could be attributed to a likely, specific cause/s.

Table 4.21: Most likely causes for initial episode of over-anticoagulation

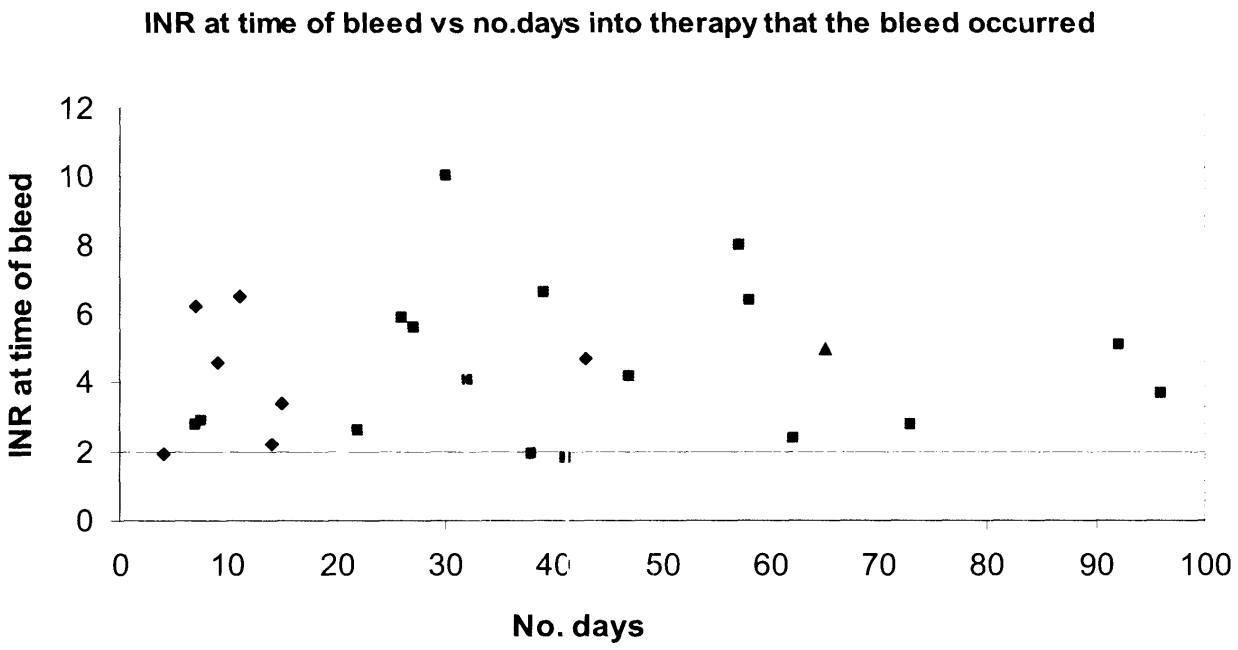
	Cause 1	Cause 2	Cause 3
Drug interaction	35	9	0
Inappropriate dose adjustment	28	10	6
Unknown cause	24	0	0
Compliance issues	11	2	1
Other	5	2	1
Decreased oral intake	4	17	2
Disease exacerbation (CCF, COPD),	4	8	3
Diarrhoea	3	4	1

Source: Analysis of study data using Excel

As shown in Table 4.21, the most likely causes of the initial episode of over-anticoagulation included drug interactions, followed by inappropriate dose adjustment, unknown causes and compliance issues, with several patients suffering from decreased

oral intake. The cause of many patients' episode of over-anticoagulation was unknown since information regarding the management or activity of the patient prior to the event was unobtainable from either the treating doctor or the patients themselves. The most likely causes of subsequent episodes of over-anticoagulation for the second and third episodes were similar to those of the initial episode. That is, for the majority of patients, the cause was recorded as unknown or drug interactions, or there were compliance issues. However, again the majority of causes was unknown due to inadequate information available to the researcher.

4.2.5 Objective 3: Determining number of major and minor (but clinically significant) bleeds and other bleeds during initial five months of treatment



Graph 4.12: Major and minor (but clinically significant) bleeds and other bleeds

Source: Analysis of study data using Excel

Code: Blue=major bleed; green=minor (but clinically significant) bleed; Red=other bleeds

4.2.5.1 Major bleeds

As shown in Graph 4.12, seven of the 294 patients (2.3%, 95% CI 0.9-4.8) incurred a major bleed during the course of the five-month study period. Of those seven patients,

three incurred a major bleed while the INR was within the range of 1.9-3.4, resulting in 57% of patients experiencing a major bleed associated with an episode of over-anticoagulation. There were no patients who incurred an intracranial bleed or suffered death as a direct result of a bleed related to warfarin during the study period.

Of the three patients who experienced a major bleed while the INR was between 1.9-3.4, all occurred between five and fifteen days after initiation of the warfarin therapy. Patient # 1 incurred a major rectal bleed five days after initiation of warfarin and post-coronary artery vein graft and mitral valve replacement, while patient # 2 experienced hematuria with blood clots 14 days post-initiation of warfarin. Patient # 3 experienced a psoas bleed/haematoma intramuscularly 15 days after commencing warfarin therapy and 11 days after having an INR=11.1. The warfarin therapy was ceased in two of the three patients, with one patient recommencing 11 days after the major bleed had occurred.

Of the four patients who experienced a major bleed associated with an episode of over-anticoagulation, three occurred between seven to eleven days post-warfarin initiation. Although the remaining one patient experienced a major bleed at 43 days after warfarin initiation, it was highly likely that this patient experienced a slow and insidious loss of blood for some time before the elevated INR was discovered and treatment was administered.

The one patient who had experienced worsening hematuria and abdominal pain had failed to seek hospital admission following advice from the GP to do so. On eventual presentation to the hospital, the patient's Hb was 74 g/L (from 112 g/L 43 days previously). It was thought the patient's worsening hematuria was secondary to radiation cystitis in the setting of clopidogrel and warfarin. Subsequently, the patient's warfarin was also ceased.

4.2.5.2 Minor but clinically significant bleeds

There were 17 patients (5.7%, 95% CI 3.4-9.0) who experienced a minor (but clinically significant bleed) or other bleed as shown in Graph 4.9. Of those 17 patients, 9 (52%) were associated with an episode of over-anticoagulation. While seven bleeds occurred during the initial month of therapy, all of these bleeds occurred during the first 96 days of warfarin therapy.

The most common bleed recorded was epistaxis, requiring medical review and/or packing/cautery, followed by blood vomit/black stools/gastric bleeding. There were two patients who experienced hematuria and one patient each who incurred hemoptysis, a blood eye, a haematoma, a bleed into the jaw and a bleed into the knee.

4.2.5.3 'Other' bleeds

There was only one patient who incurred a bleed that was categorised as 'other' bleed. The patient had failed to present for regular INR tests due to confusion as to when to present for tests in addition to what dosage of warfarin to take. After discharge from the Hospital at Home Services post-initiation of warfarin therapy, the patient had two INR tests performed during the following 60 days before the episode of over-anticoagulation and low Hb (86 g/L from 117 g/L) was discovered. It was thought the bleeding had occurred from the lower gastrointestinal tract; however, there was no overt bleeding portal and thus it was not known whether the patient was aware of any overt source of bleeding or not. Subsequently, the warfarin was ceased.

Trivial/minor, not clinically relevant bleeding was not evaluated in all patients. Thus, overall, there were 8.5% of patients (95% CI 5.5-12.2) who incurred a major bleed, a minor (but clinically significant) bleed or other bleed during the study period, with 56% of all bleeds occurring when the INR was above 4.0.

4.2.6 Objective 4: Determining patient's understanding of warfarin therapy, general health and degree of compliance prior to episode of over-anticoagulation while receiving warfarin treatment

There were 27 questions in the 'Initial Questionnaire for Patients' and 10 questions in the 'Subsequent Episode of Over-anticoagulation Questionnaire for Patients'. The 'Subsequent Episode of Over-anticoagulation Questionnaire for Patients' contained nine of the exact same questions presented in the 'Initial Questionnaire for Patients'. One extra question was formulated for the second questionnaire in order to seek any further information that patients may have wanted to give to the researcher that was not already covered by previous questions. This question was as follows: 'Is there anything about your warfarin therapy that you would like to comment on?'

The questions were formulated to seek information pertaining to three specific key areas of patient management. That is, the patient's general understanding of warfarin therapy, the patient's general health status prior to an episode of over-anticoagulation and the degree of compliance of the patient prior to an episode of over-anticoagulation. The responses to the questions were quantified while further comments made by patients were thematically analysed. The findings of the patient questionnaires are presented in the following section while an inclusive examination and discussion of the findings will be provided in the following chapter.

Of the 270 patients who had consented to being contacted by telephone each month by the researcher to ask whether they had incurred an INR>4.0 since the previous call, only 84 were aware that they had done so. There were many patients who were unaware that they had incurred an episode of over-anticoagulation, especially if they were a patient in a hospital or institution. One patient, when contacted by the researcher, thought that he/she had incurred an episode of over-anticoagulation but when accuracy of data was later checked with the patient's GP, there had not been an INR>4.0 at that stage and thus the interview concerning compliance and health status was not included in the study and only the questions pertaining to knowledge of warfarin therapy were included in the analyses.

4.2.6.1 Quantification of the knowledge of patients receiving warfarin therapy

Although there were nine closed-ended questions that pertained specifically to general warfarin knowledge of patients, six of the questions gave the patient the opportunity to further explain his/her answers. These questions were asked only at the time of the initial interview conducted after the first known episode of over-anticoagulation, except for the question pertaining to whether the patient received the same brand of warfarin from the pharmacist each time a prescription was filled, which was asked at each subsequent interview.

Table 4.22: Proportion of patients who understood the reason for commencing warfarin therapy (n=73)

	Patients	%
Yes	57	78.0
No	16	22.0
Total	73	100.0

Source: Analysis of study data using Excel and CONFINT version 4.0

Of the 57 patients (78.0%, 95% CI 66.8-86.9) who reported that they understood why they had been commenced on warfarin, 51 (89.7%) made a comment when the researcher asked them if they could further explain those reasons. Of those 51 patients, 25 (49.0%) were able to make an association with their diagnosed disease state and/or to report that the reason for commencement of warfarin was for the prevention of the formation of clots. Of the remaining 26 patients, 20 (39.2%) reported that the reason for commencing warfarin was to thin the blood and/or to prevent clots from forming but made no mention of their diagnosed disease states. Although one patient had answered yes to the question, he/she thought that the warfarin would dissolve the existing clot. While one patient had no understanding of why he had been commenced on warfarin, his wife had a good understanding. One patient reported that 'the heart didn't pump as well as it should' and another patient answered 'yes' (but would not discuss it further), and he/she was very angry to have been commenced on warfarin. Of the remaining two patients who answered 'yes', one reported that he/she 'had heart problems and needed the blood to circulate better' and the remaining patient reported that he/she had an irregular heartbeat.

Table 4.23: Proportion of patients who understand how warfarin works (n=73)

	Patients	%
Yes	54	73.9
No	19	26.1
Total	73	100.0

Source: Analysis of study data using Excel and CONFINT version 4.0

There was a moderate proportion of 73.9% patients (95% CI 62.3-83.5) who reported that they had a basic understanding of how warfarin works and further clarified their answer when asked by the researcher to explain their understanding. There were 38 (70.3%) patients who reported that warfarin thins the blood, five (9.2%) reported that warfarin

stops the blood from clotting/preventing blood clots and the remaining seven patients reported 'yes' to the question but made comments such as 'it's like rat-sak', 'it settles the blood down', 'it keeps the blood from sticking to the arteries', 'it's a poison, I've read about it in the booklets' and 'think so' (but wouldn't say), indicating that these patients did not have a good understanding of how warfarin worked.

Table 4.24: Proportion of patients aware of main side effects of warfarin (n=73)

	Patients	%
Yes	29	39.7
No	44	60.3
Total	73	100

Source: Analysis of study data using Excel and CONFINT version 4.0

Of the 29 patients (39.7%, 95% CI 28.4-51.8) who reported that they were aware of the main side effects of warfarin and made further comment when asked by the researcher to list them, 20 (69.0%) reported bleeding as its main side effect. Of the remaining three patients who made a comment, one patient reported 'vomiting, nightmares, tiredness and shortness of breath', one patient reported 'bruising and that sort of thing' and the remaining patient reported 'bruising and brown urine' were the main side effects of warfarin.

Table 4.25: Proportion of patients who understood why dose may change (n=73)

	Patients	%
Yes	59	80.8
No	14	19.2
Total	73	100.0

Source: Analysis of study data using Excel

The majority of patients reported that they had an understanding of why their dose may change and made a further comment when asked by the researcher to clarify what those reasons may be. There were 40 patients (54.8%) who reported that changes in dosages were due to changes in the INR results. Of the remaining patients who made comments, one reported that 'it has to reach a certain level', two patients reported 'according to the thickness of the blood', one patient reported environmental factors and alcohol, one

patient reported types of foods and the remaining patient reported that it was due to ill health.

Table 4.26: Proportion of patients who kept a record of their blood tests and warfarin doses (n=73)

	Number	%
Yes	52	71.2
No	21	28.8
Total	73	100.0

Source: Analysis of study data using Excel and CONFINT version 4.0

While 52 patients (71.2%, 95% CI 59.4-81.2) reported that they kept a record of their INR results and warfarin doses, almost one third of the patients interviewed did not.

During the course of the study period, patients were asked to provide the researcher with their INR results, warfarin dosages and corresponding dates if known, when contacted each month. Of the 294 patients/carers of patients in the study, 180 (61.2%, 95% CI 55.3-66.8) kept a record of their warfarin management and were able to provide INR results and dosages with corresponding dates to the researcher. However, not all information provided correlated with data later checked with the medical records provided by the hospitals/GPs. There were 25 patients (13.8%) whose records provided to the researcher did not correlate with the doctor's records when checked on completion of the study period.

Only 77 patients (26.2%, 95% CI 21.2-31.6) were aware of their current dose of warfarin when contacted, but did not keep a record and were not aware of their INR results. There were 13 patients (4.5%) who were not aware of their INR results or dosages and kept no record of either and the remaining 24 patients (8.1%) were not contacted because they did not wish to be or the researcher was not able to reach them.

Table 4.27: Proportion of patients who received the same brand of warfarin every time from the pharmacist (n=85)

	Patients	%
Yes	63	74.1
No	3	3.5
Uncertain	19	22.4
Total	85	100.0

Source: Analysis of study data using Excel

Table 4.27 shows that almost two thirds of the patients reported that they received the same brand of warfarin from the chemist every time. Of those 19 patients who were uncertain, four patients were in hospital at the time of the interview and had yet to obtain warfarin from the chemist. Likewise, several other patients who were uncertain had only been recently discharged home and had yet to fill a successive prescription for warfarin tablets from the pharmacist.

Table 4.28: Proportion of patients being aware of the signs and symptoms of bleeding caused by warfarin (n=73)

	Patients	%
Yes	46	63
No	27	37
Total	73	100

Source: Analysis of study data using Excel and CONFIDENT version 4.0

Of the 46 patients (63.0%, 95% CI 50.9-74.0) who reported that they knew what the signs and symptoms of bleeding caused by warfarin were, only 37 were able to list some of the signs and symptoms when asked to do so by the researcher. There were eight (21.7%) patients who could name one sign/symptom. 12 (32.4%) patients who could name two signs/symptoms, a further eight (21.7%) patients who could name three signs/symptoms, three (8.1%) patients who could name four signs/symptoms and five (13.5%) patients who could name five signs/symptoms. No patients could name all the obvious and less obvious signs and symptoms of bleeding caused by warfarin. There was one patient who reported giddiness as a sign/symptom of bleeding. The most common signs and symptoms named by the patients included the following, the number in parentheses indicating the number of times the symptom had been mentioned:

1. Cuts/Scratchers may bleed more (16)
2. Blood in urine or stools (16)
3. Bruising (15)
4. Nose bleeds (9)
5. Bleeding gums (6)
6. Bleeding to bowel only (5)
7. Increased pain, internal bleeding, gastric bleeding and bleeding from the ears (1)

Table 4.29: Proportion of patients to have experienced any of the signs and symptoms of bleeding while on warfarin (n=73)

	Patients	%
Yes	31	42.4
No	42	57.6
Total	73	100.0

Source: Analysis of study data using Excel and CONFINT version 4.0

Table 4.29 shows that it was not uncommon for patients to report signs and symptoms of some minor bleeding while on warfarin (42.4%, 95% CI 30.9-54.5). The most common signs and symptoms reported included nosebleeds, followed by bruising, bleeding from the mouth/gums, cuts bleeding more, brown colour/blood in urine, blood in stools and haemorrhoids bleeding. There were single reports of bleeding from the ear, into the knee, reddish/brown vomit and a black stool. Of the 31 patients who reported sign/s and symptom/s to the researcher, 18 (58.0%) reported that they informed their treating doctor, while the remaining 13 (42.0%) patients did not inform their treating doctor. The main reason given why the treating doctor was not informed of the signs/symptoms was because the patient did not think it was important to do so.

Table 4.30: Proportion of patients being aware of the length of time the warfarin therapy was required (n=73)

	Patients	%
Yes	42	57.6
No	31	42.4
Total	73	100.0

Source: Analysis of study data using Excel

Table 4.30 indicates that almost half of the patients were not aware of the length of time the warfarin therapy was required.

4.2.6.2 Quantification of the degree of compliance of patients taking warfarin therapy

There were 13 questions which pertained to the degree of compliance of patients taking their warfarin. They included six closed-ended questions, six open-ended questions and one question using the Likert scales. Seven questions were repeated in the 'Subsequent Episode of Over-anticoagulation Questionnaire for Patients'. All initial and subsequent interviews of patients who incurred an episode of over-anticoagulation are included in the following data analyses.

Table 4.31: Proportion of patients who reported major changes in their normal eating habits in the week prior to an INR>4.0 (n=83)

	Patients	%
Yes	26	31.3
No	57	68.6
Total	83	100.0

Source: Analysis of study data using Excel and CONFINT version 4.0

A relatively high proportion of patients (31.3%, 95% CI 21.5-42.4) reported that there had been a substantial change in their normal eating habits in the week prior to the episode of over-anticoagulation. Of the 26 patients who recorded a change in their normal eating habits, 11 (42.3%) reported that there had been a substantial increase in their alcohol intake and 15 (57.7%) patients reported that there had been a substantial decrease

in their food intake due to nausea or little to no appetite. One patient had recorded both an increase in alcohol intake and a decrease in food intake.

Table 4.32: Proportion of patients who let the doctor managing the warfarin treatment know about all of the tablets they were taking including vitamins, homeopathic medications, herbal preparations and food supplements (n=84)

	Patients	%
Yes	81	96.4
No	3	3.6
Total	84	100.0

Source: Analysis of study data using Excel and CONFINT version 4.0

The majority of patients (96.4%, 95% CI 89.9-99.2) reported that they let the doctor managing their warfarin know about all medications being taken. Only three (3.6%) patients failed to inform their treating doctor of all medications. Those medications were OTC medications and included calcium tablets, vitamin B, E and C, omega 3 fish oil tablets, flaxseed oil tablets, Centrum and ginkgo tablets.

Table 4.33: Proportion of patients who had any new tablets commenced in the week prior to the INR>4.0 (n=71)

	Patients	%
Yes	24	33.8
No	47	66.2
Total	71	100.0

Source: Analysis of study data using Excel

Of the 72 patients interviewed, one did not know whether he/she had been commenced on any new tablets or not and was thus omitted from the analysis. Only one patient who had been commenced on a new tablet failed to inform the doctor managing their warfarin treatment.

Table 4.34: Proportion of patients who had an increase in any medicines that are only taken occasionally, e.g. painkillers (n=71)

	Patients	%
Yes	11	15.4
No	60	84.6
Total	71	100.0

Source: Analysis of study data using Excel and CONFINT version 4.0

Of the 72 patients interviewed, one did not know whether he/she had increased any occasional medicines or not and was thus omitted from the analysis. Of the 11 patients (15.4%, 95% CI 7.9-26.0) who reported that they had increased their occasional medicines, paracetamol was the most common medicine taken, with all patients taking a paracetamol-based medication. Those medications included panadeine-forte and paracetamol. One patient reported taking as little as four tablets over two days while the remaining 10 patients reported taking from four to eight tablets per day for one to two days to a week.

Table 4.35: Proportion of patients who informed the doctor managing the warfarin treatment if they had increased their occasional medicines (n=11)

	Patients	%
Yes	9	81.9
No	2	18.1
Total	11	100.0

Source: Analysis of study data using Excel

Table 4.35 shows that the majority of patients who increased their occasional medicines reported it to their treating doctor.

Table 4.36: Proportion of patients taking their warfarin at approximately the same time each day (n=73)

	Patients	%
Yes	72	98.6
No	1	1.4
Total	73	100.0

Source: Analysis of study data using Excel and CONFINT version 4.0

Table 4.36 indicates that almost all patients (98.6%, 95% CI 92.6-99.9) were compliant in taking their warfarin at approximately the same time each day.

Table 4.37: Proportion of patients who missed a dose (n=84)

	Patients	%
Never	71	84.5
Once/month	6	7.2
Other	7	8.3
Total	84	100.0

Source: Analysis of study data using Excel

A large proportion (84.5%, 95% CI 74.9-91.4) of patients reported that they never missed a dose, indicating a high level of compliance with the treatment from those patients interviewed. Patients in the 'other' category reported that they were not sure whether they had missed a dose or not. All the patients who did report missing a dose said that they waited until the following day at the usual time to take their warfarin again.

Although the patients interviewed reported a high level of compliance with the therapy, there were several incidences where patients reported less than satisfactory compliance to the researcher when contacted each month. A patient reported to his/her GP that he/she had ceased the warfarin days beforehand for no known reason. Subsequently, the GP re-commenced the patient on warfarin. A further two patients adjusted their own doses unbeknown to the treating doctor, with one patient indicating to the researcher that he/she was concerned about the amount of warfarin prescribed and so if she thought the INR was too high, she would reduce the dosage for a few days. There were no INR results recorded above 3.0 at any stage for this patient during the study period. The remaining patient's carer also reduced the prescribed dose unbeknown to the treating doctor when an INR was recorded as 3.9. The doctor prescribed a dosage of 5 mg from 6 mg while the patient's carer gave the patient 2 mg daily. Subsequently, the INR results were recorded below 2.0 for the following six tests (seven weeks).

Another patient who was prescribed 4 mg daily took 3 mg daily for several weeks because he/she had run out of 1 mg tablets and failed to present for an INR for six weeks whereupon the INR was recorded as 2.0. Lastly, two patients ceased their own warfarin due to an inability to afford the medication. Both patients had been diagnosed with DVT/PE.

Table 4.38: Means by which doctor lets patient know what dose of warfarin to take (n=69)

	Patients	%
Telephone	53	76.8
Other	15	23.2
Total	69	100.0

Source: Analysis of study data using Excel

Fifteen (23.2%) patients reported receiving their instructions for dosage either direct from the doctor when present in the surgery or, if in-patients at an institution, receiving their dosage from nursing staff. There were four patients who were not yet discharged from hospital after being initiated on warfarin and thus these patients received their warfarin dose from the registered nurses and were not included in the analysis.

Table 4.39: Instructions for dose of warfarin to be used were found easy to follow or not by patient (n=80)

	Patients	%
Very easy	48	60.0
Easy	31	38.7
Very difficult	1	1.3
Total	80	100.0

Source: Analysis of study data using Excel and CONFINT version 4.0

At the time of the interview four patients were still in hospital and thus their answers to the question were omitted from the analysis because the registered nurse administered the required dose. There was a combined proportion of patients of 98.7% (95% CI 93.2-99.9) who reported that the instructions for what dose of warfarin to take was either '*very easy*' or '*easy*' to understand. However, of the 48 patients who reported the instructions to be '*very easy*', three patients took incorrect dosages, all immediately post-discharge from the hospital. Patient # 1 reported accidentally taking a dose of warfarin twice a day for some time due to incorrect labelling of the bottles by the discharging hospital. The patient reportedly took 3 mg warfarin twice a day thinking it was sotalol. The patient incurred three episodes of over-anticoagulation, the highest being 7.4, before the mistake was identified.

Patient # 2, who appeared confused as to the instructions on discharge from the hospital, was reportedly given ten 1 mg tablets and ten 3 mg tablets and mistakenly took 10 mg, instead of 4 mg the first night home, thinking that he/she was given four days' worth of warfarin only and not knowing what dose to take, took the amount given divided by four. The patient reported that the hospital had not told him/her what dosage to take each night. The next day the patient, not feeling well, notified his/her GP and was told to omit the warfarin for the next two days and then have an INR test. The next INR was 4.9 two days after the patient took the 10 mg warfarin. During the course of the five-month study period the patient reported taking 2 mg of warfarin for some time, but when data were checked via the GP's medical records, the patient was recorded as being prescribed 3 mg and 4 mg daily. It would appear that although the patient thought the dosage instructions were '*very easy*' to follow, incorrect doses were taken on several occasions.

Patient # 3, by his/her own admission, was confused on discharge from the treating hospital and mistakenly took 13 mg of warfarin instead of the prescribed 5 mg on the first night home. As a result the patient incurred an INR=7.6 four days later, was readmitted to the hospital and administered vitamin K and Prothrombinex-HT. The patient's Hb dropped from 106 g/L on admission to hospital, to 86 g/L two days later and the patient required a blood transfusion of two units of red blood cells. The patient admitted that he/she was initially very confused as to the dosage instructions given but later reported a clear understanding of the instructions and was extremely careful to take the correct dosage. Despite this, the patient incurred an overall total of five episodes of over-anticoagulation during the five-month study period.

There was one patient who reported that the instructions were '*very difficult*' to follow and consequently incurred an episode of over-anticoagulation 14 days after discharge from hospital and was subsequently readmitted for treatment of over-anticoagulation. On initial discharge from the hospital, the patient did not attend the Hospital at Home Services and was discharged directly to the care of his/her GP. The patient reported being unsure of when to contact the GP and when doing so, found it difficult to reach the GP. The patient was also unsure of what dose of warfarin to take and subsequently failed to take any at times and at other times took warfarin when it should have been omitted. Consequently, the patient omitted a dose of warfarin when the INR was 2.1 and took 5 mg of warfarin when the INR was 4.8. The highest INR was recorded at 6.2 when the patient was readmitted to the hospital to receive two units of FFP. The patient was

eventually discharged home in the care of the Hospital at Home Services who managed his/her warfarin doses and INR results for the next seven days before discharging him/her into the care of the GP again.

Finally, a patient who reported to the researcher that he/she had incurred an INR>4.0 – who had not as it turned out when the data were later checked with the GP – reported being unclear of the instructions to follow. The patient reported that the GP had not informed him/her when next to have an INR test or what dose of warfarin to take in the meantime. Consequently, the patient did not have another INR test for the next 35 days when it was discovered in the OPD that the patient's INR was 5.2 and the Hb was 86 g/L. The patient was readmitted to hospital to receive two units of packed cells and investigate the cause of the low Hb. Subsequently the warfarin was ceased shortly thereafter.

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

There were five closed-ended questions pertaining to the patient's health status prior to an episode of over-anticoagulation, with two of the questions allowing for further comments. All initial and subsequent interviews of patients who incurred an episode of over-anticoagulation are included in the following data analyses.

Table 4.40: Proportion of patients who experienced diarrhoea for at least two consecutive days (n=84)

	Patients	%
Yes	11	13.1
No	73	86.9
Total	85	100.0

Source: Analysis of study data using Excel

Table 4.40 indicates that the majority of patients did not experience any diarrhoea for at least two consecutive days prior to the episode of over-anticoagulation. Of the eleven patients who had reported having diarrhoea, five (45.5%) had reported it to their treating doctor, three (27.2%) had not reported it, and it was not known whether the remaining three (27.3%) had reported it to their treating doctor or not.

Table 4.41: Proportion of patients who experienced vomiting for at least two consecutive days (n=84)

	Patients	%
Yes	3	3.5
No	81	96.5
Total	84	100.0

Source: Analysis of study data using Excel

Of the three patients who did report vomiting, two reported it to their treating doctor while one patient did not. The patient who failed to report it to their treating doctor reported that he/she had felt like vomiting after food, and had at times done so, for the previous two weeks. The vomit was described by the patient as black/brown in colour but had not reported it because he/she was not aware that it might have been old blood or of any significance. However, the patient did report to their treating doctor that he/she felt generally unwell for the previous two weeks with central chest pain associated with deep inspiration and a painful leg. The patient incurred an INR=4.2 at this time and subsequently the warfarin was omitted while several investigations were conducted. The patient was diagnosed with an invasive adenocarcinoma of the stomach with bilateral pleural effusions and a thrombus to the common femoral vein. Consequently, the warfarin was ceased.

Table 4.42: Proportion of patients with an increased temperature or fever that they were aware of (n=83)

	Patients	%
Yes	7	8.4
No	76	91.6
Total	83	100.0

Source: Analysis of study data using Excel and CONFINT version 4.0

Of the 83 patients who were interviewed, a small proportion (8.4%, 95% CI 3.4-16.6) only reported a temperature or fever that they were aware of in the previous week prior to the episode of over-anticoagulation. Three patients reported it to their treating doctor while two patients failed to report it. It was not known whether the remaining two patients reported their temperature to the doctor or not.

Table 4.43: Proportion of patients with a newly diagnosed illness (n=83)

	Patients	%
Yes	18	21.6
No	65	78.4
Total	83	100.0

Source: Analysis of study data using Excel

As shown in Table 4.43, only a small proportion of 18 (21.6%) patients reported being diagnosed with a new illness, with the doctor managing their warfarin treatment being aware of the new illness in 16 (88.9%) of those patients.

Table 4.44: Proportion of patients with any other health problem not mentioned (n=83)

	Patients	%
Yes	9	10.8
No	74	89.2
Total	83	100.0

Source: Analysis of study data using Excel and CONFINT version 4.0

There was only a small proportion of nine (10.8%) patients who experienced any other health problems not already mentioned in the questionnaires. Of those nine patients, six reported the problems to their doctor managing their warfarin treatment.

There were three patients who did not inform their treating doctor. Of those three patients, patient # 1 reported minor problems of nausea, feeling tired and not sleeping well. Patient # 2, who did not speak English well and was subsequently interviewed via the daughter, reported her father as feeling unwell with no appetite for several days and passing black, tarry, very smelly stools for three days prior to a collapse at home. Although the Hospital at Home Services nurses were visiting the patient each day to manage the warfarin, the patient failed to inform the nursing staff of any problems, was not aware of the signs and symptoms of bleeding and therefore did not realise the significance of black stools. The patient was readmitted to hospital in a non-responsive state, via an ambulance with a Hb of 68 g/L, and melena. Vitamin K, Prothrombinex-HT, FFP, five units of packed cells and intravenous pantoprazole were administered to the patient on admission to hospital. It was noted that the patient had been taking aspirin, amiodarone, ibuprofen and warfarin along

with several other medications at home, although the warfarin had been withheld for the previous seven days because the INR had peaked at 6.5. An endoscopy revealed the presence of six active gastric ulcers and consequently, the warfarin was ceased. The patient was discharged home three days later.

Patient # 3, who failed to inform the treating doctor of an additional health problem, knocked his/her arm and was attending to the care of it at home with daily dressings. Approximately one week later, the patient woke up to find a blood-soaked bandage, bedclothes and bed. The patient was readmitted to hospital with an INR of 5.1 and a Hb of 109 g/L. It was discovered that the patient had suffered from a urinary tract infection the week before and had been commenced on antibiotics for treatment with no adjustment to the warfarin dosage. No transfusion was required and the patient was discharged home in the care of the Hospital at Home Services nursing staff.

4.2.7 Objective 5: Determining current trends and concepts in medical management of patients receiving warfarin therapy in hospital and community setting

The 'Initiation of Warfarin Therapy Questionnaire for Doctors' consisted of 25 structured questions that sought to obtain information regarding current trends and concepts of warfarin management by medical practitioners in both the hospital setting and the community. The questions consisted of 18 closed-ended questions and seven open-ended questions. The questionnaire was specifically formulated to obtain factual data that could be analysed by empiric-analytical means, i.e., that was quantifiable, while allowing for a greater range of responses to reveal the full and true nature of the complex phenomenon under investigation.

There were some questions which were randomly missed by doctors when completing the questionnaire and thus the sample size varied throughout the analyses. Because different questions were missed, it was assumed that it was not because of difficulty in understanding or interpreting the questions but more due to either time constraints to complete the questionnaire or thinking that the question was not pertinent to them. Both hospital-based doctors and GPs completed the same questionnaire. The findings of the doctor questionnaires are presented in the following section while an inclusive

examination and discussion of the findings will be given in the following chapter. All data have been collectively analysed, with no individual ideas or concepts targeted.

Doctors were first asked to provide simple demographic information to ensure that the sample captured a wide and varied range of responses.

Table 4.45: Doctor designation (n=146)

Place	Designation	Doctors	%
General Practitioner		99	67.8
Hospital-based	Medical Intern	20	13.7
	Resident Medical Officer	17	11.7
	Registrar	8	5.5
	Other	2	1.3
Total		146	100.0

Source: Analysis of study data using Excel

As shown in Table 4.45, the majority of doctors (67.8%) to complete the questionnaire were GPs.

Table 4.46: Proportion of GPs who, in 2005, attended any of the thrombolytic / anticoagulant educational programs by the National Prescribing Service (n=99)

	GPs	%
Yes	22	22.2
No	77	77.8
Total	99	100.0

Source: Analysis of study data using Excel

Table 4.46 indicates that a small proportion of GPs only reported attendance at any of the thrombolytic/anticoagulant educational programs by the National Prescribing Service in 2005.

Table 4.47: Proportion of doctors who routinely set an INR target prior to commencement of warfarin therapy for each patient (n=146)

	Doctors	%
Yes	143	97.9
No	3	2.1
Total	146	100.0

Source: Analysis of study data using Excel and CONFINT version 4.0

An overwhelming majority of doctors (97.9, 95% CI 94.1-99.5) reported that they routinely set a target INR prior to commencement of warfarin therapy for each patient. Of the three doctors who reported that they did not, one reported that advice for a target range was taken from the consulting specialist and the remaining two did not make a comment.

Of the 52 doctors who specifically reported that they set a target range for AF, 43 (82.6%) reported that they set the range between 2.0-3.0. Three doctors reported that they set the target range between 2.0-2.5, three set the range between 1.9-2.5 and the remaining three doctors set their target ranges between 2.0-3.5, 1.8-2.6 and 2.0 respectively.

Of the 38 doctors who specifically reported that they set a target range for DVT/PE, 32 (84.2%) reported that they set the range between 2.0-3.0. Of the remaining six doctors, each set target ranges as follows: PE:2.5-3.5, DVT/PE:1.5-3.0, DVT:3.0-3.5, 2.0-4.0, 2.5-4.0 and for a recurrent PE:3.0-4.0.

Of the 97 doctors who did not specify which condition the target range was set for but rather reported a general range that was set, 60 (61.8%) doctors reported 2.0-3.0 as the general range. There were 15 (15.5%) who reported that the target range was dependent on the indication for warfarin and co-morbidities of the patient but did not specify a range, while nine (9.3%) reported a general target range between 2.0-4.0. Of the remaining 13 responses, four set the general target range between 2.0-3.5, three set the general target range between 2.0-2.5, two set the target at an exact 2.5, a further two set the target between 2.5-3.0 and one set the target at 2.5-3.5.

Of the 53 doctors who specifically reported a set target range for valve replacements, 26 (49.0%) reported that they set the general target for all valves between 2.5-3.5. There were five doctors who reported that they set the target range for high-risk prosthetic valves between 3.0-4.0, while five doctors reported setting a target range between 3.0-4.0

for valves in general. There were three doctors who reported a range of 2.0-3.0 for aortic mechanical valves while another three indicated a range in the mid threes as being the set target range for artificial valves. Of the remaining 12 doctors, two indicated a target range between 2.5-4.0, a further four indicated a range between 3.0-4.5 as being set especially for the 'older' style valves, two set the target range between 2.0-3.0 for all valves and the remaining three reported target ranges between 3.5-4.5 for aortic valve replacements (AVR) and mitral valve replacements (MVR), 2.0-2.5 for AVR, and 3.0-3.5 for prosthetic valves while one set the target at 2.5-3.5 for low risk valve replacements.

Of the remaining responses regarding the setting of target ranges, one doctor set the range between 1.5-2.5 for the treatment of ischaemic heart disease (IHD), another doctor set the range between 1.5-2.5 for peripheral vascular disease (PVD) while one doctor set the target between 3.0-4.0 for PVD and one reported to follow the laboratory protocols for INR target ranges.

Table 4.48: Proportion of doctors who would alter the normal target range in certain situations (n=143)

	Doctors	%
Yes	118	82.5
No	25	17.5
Total	143	100.0

Source: Analysis of study data using Excel

Even though an overwhelming proportion of doctors reported that they set a target range prior to commencement of warfarin therapy, a large proportion (82.5%) reported that they would also alter the range in certain situations.

Table 4.49: Situations where doctors would alter the target range

Indication	Doctors	%
Valve replacements	37	23.3
Specialist advise	19	11.9
Elderly & Frail patient	18	11.4
Clinical profile & co-morbidities	17	10.6
Increased bleeding risk	15	9.5
Recurrent thromboembolic event while on warfarin	12	7.5
Unacceptable bleeding at target range	9	5.7
High falls risk	8	5.0
Recurrent DVT/PE	5	3.1
Patient compliance	3	1.9
Antiphospholipid syndrome	3	1.9
Other	13	8.2
Total	159	100.0

Source: Analysis of study data using Excel

Of the 118 doctors who reported that they would alter the target range, many reported more than one situation in which they would do so, while others did not clarify when they would change the target range except to say that they would. The most common reason given for altering the target range was to address the change in their situation for patients who had undergone a heart valve replacement.

Other reasons reported included clotting tendencies or increased risk of embolism prior to cardioversion, minor surgery, other medications, heart valve with AF, only within the set target range, prevention of recurrent MI, underlying genetic/haematological predisposition and ischaemic CVA with AF and evidence of atrial mural thrombi.

Table 4.50: Proportion of doctors who determined the duration of the warfarin therapy for each patient in advance of commencing therapy (n=142)

	Doctors	%
Yes	79	55.7
No	13	9.1
Sometimes	50	35.2
Total	142	100.0

Source: Analysis of study data using Excel

Table 4.50 shows that over half of the doctors (55.6%) determined the duration of warfarin therapy and a little over one third (35.2%) sometimes determined the duration. Of those doctors who reported that they did not determine the duration of therapy and made a comment as to why they did not, most reported that they did not initiate patients on warfarin and/or that the specialist/hospital usually set the duration of the warfarin therapy.

Table 4.51: Proportion of doctors who, with regard to warfarin initiation, use a recognised algorithm or were guided by their own clinical judgement (n=142)

	Doctors	%
Algorithm	63	44.3
Clinical judgement	57	40.1
Both	19	13.8
Warfarin not initiated by GP	3	1.8
Total	142	100.0

Source: Analysis of study data using Excel and CONFINT version 4.0

There were 29 (61.7%) of 47 hospital-based doctors and 34 (36.9%) of 92 GPs who reported using a recognised algorithm when initiating warfarin, resulting overall in a total proportion of 44.3% of doctors who utilised a recognised algorithm. Eight (17.0%) of 47 hospital-based doctors and 49 (53.2%) of 92 GPs reported using their own clinical judgement when initiating warfarin, resulting in a total proportion of 40.1% (95% CI 32.0-48.6) doctors who used their own clinical judgement when initiating warfarin. Finally, 10 (21.2%) of the hospital-based doctors and nine (9.7%) of GPs reported using both a recognised algorithm and their own clinical judgement when initiating warfarin. This resulted in an overall total proportion of 13.3% (95% CI 8.2-20.1) doctors who used

both. Three GPs reported that they did not initiate patients on warfarin at all and four GPs failed to answer the question.

It would appear from the above findings that hospital-based doctors utilised a recognised algorithm more often than using either their own clinical judgement or both when initiating patients on warfarin therapy, while GPs used their own clinical judgement more often than utilising an algorithm or both. Comments made by those doctors who utilised an algorithm, both hospital-based doctors and GPs, revealed that many used the Flinders Medical Centre (FMC) algorithm, which was an age-adjusted protocol. Of the 63 doctors who reported using an algorithm to initiate their patients on warfarin, three said that they used their own clinical judgement if the INR rapidly or grossly changed or if there were other factors to consider, such as a patient taking amiodarone. One doctor reported that he/she modified the algorithm depending on other medications the patient was taking, the bleeding risk or if there was a perceived problem with compliance, as did other doctors who reported using both algorithm and their own clinical judgement.

Of those doctors who reported using their own clinical judgement only, several deemed using an algorithm too restrictive because there were many other variables that had to be taken into consideration, especially in general practice, such as patient compliance, co-morbidities, concurrent medications, co-existing illnesses, past history, the weight of the patient, liver disease, renal function or CCF. Additionally, those GPs initiating patients on warfarin in the surgery reported that because there was usually no urgency in attaining rapid anticoagulation, a more gentle approach was followed.

Table 4.52: Proportion of doctors who routinely assess each patient for risk of bleeding prior to the commencement of warfarin therapy (n=141)

	Doctors	%
Yes	123	87.2
No	18	12.8
Total	141	100.0

Source: Analysis of study data using Excel and CONFINT version 4.0

A major proportion (87.2%, 95% CI 80.5-92.2) of doctors reported that they routinely assessed each patient for the risk of bleeding prior to the commencement of warfarin therapy. Those doctors who reported that they did not assess for risk of bleeding, and made a comment as to why, reported that they did not or only rarely initiate patients on

warfarin and/or it was thought the assessment was attended to by those initiating the patient.

Of the 123 doctors who reported that they routinely assessed each patient for risk of bleeding, 95 (77.2%) included the bleeding history of the patient as a factor to consider, 62 (50.4%) included concomitant medications, 53 (43.8%) included a falls risk, 38 (30.8%) included the age of the patient, 30 (24.7%) included the cognition of the patient and 29 (23.5%) included the patient's medical history. There were 19 (15.5%) doctors concerned with the blood picture of the patient, 18 (14.7%) who included whether the patient was perceived as being compliant or not, 15 (12.1%) who were concerned with both co-morbidities and recent surgery and 13 (10.6%) who were concerned with alcohol intake. Nine (7.3%) doctors took blood disorders, liver disease and lifestyle into account, six (4.9%) took hypertension into account, five (4.1%) considered the diet of the patient and four (3.2%) took the indication for warfarin into account. The remaining factors reported included the patient's general health, previous myocardial infarctions, the stability of the INR, allergies, education, malignancy, eyesight, gender and genetics.

Table 4.53: Proportion of doctors who use a scoring system to stratify the risk of bleeding (n=141)

	Doctors	%
Yes	2	1.4
No	139	98.6
Total	141	100.0

Source: Analysis of study data using Excel and CONFINT version 4.0

Table 4.53 shows that almost all doctors (98.5%, 95% CI 94.9-99.8) reported that they did not use a scoring system to stratify the bleeding risk. Some doctors reported that they would be interested in using a scoring system if there was one available, while others reported that they had not seen a system that was proven to be reliable.

Barriers faced by doctors in the management of warfarin therapy

Of the 131 doctors who completed the question, a large proportion (89.3%) reported that they faced barriers in the management of warfarin therapy. Of the 14 doctors who reported no barriers, two reported that they used POC monitoring which saved time and

avoided confusion with patients. The barriers faced by the remaining 117 doctors fell into three broad categories: patient-orientated, medication-orientated and system-orientated barriers.

Patient-orientated barriers

There was an overwhelming report of barriers to warfarin management associated with patient compliance and general understanding of warfarin therapy. Largely, the major concerns lay with patients not presenting for regular INR tests and not being able to be contacted by the doctor, or contacting the doctor themselves, to obtain instructions for dosages and results.

Doctors were also concerned with the amount of confusion surrounding the treatment, that is, incorrect dosage taken and missed dosage, dietary changes, alcohol intake and OTC medications that are taken without informing the doctor. Early dementia associated with the elderly patient added to the confusion, with the patient unable to manage their warfarin dosage or understand what an INR was. One GP reported compliance and understanding in the elderly population as being a significant problem and the increase in anticoagulation for the treatment of AF had caused, in his opinion, significant morbidity among elderly patients.

Additionally, several doctors reported the fear of warfarin held by some patients impacted on their decision to commence warfarin, on compliance and understanding, and increased their sense of dissatisfaction with taking the drug. Other barriers included difficulty in finding transport to and from the surgery or laboratory by patients, patients living alone with little or no help, language barriers, education barriers, maintenance of the same brand of warfarin and difficulties incurred when the patient decided to go on a trip or holiday away.

Medication-orientated barriers

Although not as overwhelming as the barriers of patient compliance and understanding, the barriers of polypharmacy and medication interactions were reported as the major medication-orientated barrier. The next most frequently reported barrier was the unexplained fluctuations and variations in the INR and the frustrations associated with

this. Risk of bleeding, the age of the patient and the risk of falls and the need for constant monitoring and balancing of the monitoring with the need to know the INR were also reported as barriers. Other barriers included difficulty in management on weekends and public holidays when there is no doctor available, acute illness of the patient, surgery, worsening heart failure and patient resistance to warfarin.

System-orientated barriers

The most commonly reported system-orientated barrier was that the management of warfarin was time consuming and cumbersome. Barriers that constituted this included difficulty for the patient to obtain either access to the GP for initial or follow-up appointments or transport to surgery/laboratory to have an INR test performed. Additionally, receiving INR results back in a timely manner was reported as a barrier as was difficulty in contacting patients, determining correct dosages, which were often found to be incongruent with what the patient had been taking if dosage was unchanged, and time spent by staff contacting patients to relay instructions. Three doctors reported that there was a lack of POC testing available which would aid the situation by reducing confusion in dosing, time in contacting patients and subsequently reduce costs.

Additionally, several doctors reported inadequate information on the patient's discharge from hospital. That is, no records of INR results and warfarin dosages were forthcoming if warfarin therapy had commenced in hospital. Furthermore, there was perceived difficulty encountered when patients were discharged home with no support or help if the Hospital at Home Services was fully booked.

Table 4.54: Proportion of doctors who periodically re-evaluate patient's harm:benefit ratio for warfarin during course of therapy (n=145)

	Doctors	%
Yes	115	79.3
No	30	20.7
Total	145	100.0

Source: Analysis of study data using Excel and CONFINT version 4.0

A moderate proportion (79.3%, 95% CI 71.8-85.5) of doctors reported that they periodically re-evaluated the patient's harm:benefit ratio for warfarin during the course of

therapy. Of the 30 doctors who reported that they did not, almost half (14) were hospital-based doctors and referred to the GP to follow up on the patient.

Table 4.55: Proportion of doctors who inform patient of risk of bleeding on commencing warfarin therapy (n=145)

	Doctors	%
Yes	140	96.6
No	5	3.4
Total	145	100.0

Source: Analysis of study data using Excel and CONFINT version 4.0

The overwhelming majority of doctors (96.5%, 95% CI 92.1-98.8) reported that they informed the patient of the risk of bleeding on commencing warfarin therapy. Of the five doctors who reported that they did not inform the patient, four reported that they did not initiate patients on warfarin therapy and relied on the hospital pharmacist to inform the patient. One doctor reported that although he/she did not initiate patients on warfarin, he/she did inform the patient of the risk of bleeding during the course of therapy.

Table 4.56: Proportion of doctors able to predict or foresee instability of an INR (n=146)

	Doctors	%
Yes	42	28.8
No	70	47.9
Sometimes	34	23.3
Total	146	100.0

Source: Analysis of study data using Excel and CONFINT version 4.0

Of the combined proportion of 52.0% (95% CI 43.6-60.3) of doctors who reported 'yes' and 'sometimes' to the question whether they were able to predict instability of the INR, a change in medications/drug interaction was reported overwhelmingly as the most common contributing factor. The most commonly reported medications to impact on the stability of the INR were the introduction of antibiotics, amiodarone, OTC medications and polypharmacy. The second most commonly reported factor to influence the stability of the INR was patient compliance, followed by a change in diet or an episode of acute illness. The presence of co-morbidities, such as chronic heart failure, chronic obstructive

pulmonary disease or previous bleeding was reported to impact on the stability of the INR, as did the age of the patient, alcohol intake, changes in lifestyle and the general stability/instability of the INR.

Table 4.57: Proportion of doctors who, if INR>4.0, attempt to identify the cause (n=143)

	Doctors	%
Yes	128	89.5
No	15	10.5
Total	143	100.0

Source: Analysis of study data using Excel and CONFINT version 4.0

Table 4.57 shows that the majority of doctors (89.5%, 95% CI 83.2-94.0) attempted to identify the cause of an INR>4.0. Of the small proportion who reported that they did not, most did not clarify why, but of those doctors who did, most thought it was not practical to spend time investigating, unless the high INR was persistent or was much higher than 4.0.

Of the doctors who reported making an attempt to identify the cause of an INR>4.0, the majority looked towards other medications/drug interactions as the main cause. Thereafter, factors that were considered included significant changes in the patient's diet, including alcohol intake, mistakes made in dosage and general compliance issues and changes in the patient's general health including acute illnesses and lifestyle changes. Other less often reported factors included the pattern of the INR thus far, changes in liver function tests, the education of the patient and general history. Several doctors reported that although they investigated the cause, often it was not found.

Table 4.58: Proportion of doctors who said they would attempt to identify the cause of INR>4.0 if identifiable, would attempt to correct the cause (n=137)

	Doctors	%
Yes	132	96.3
No	5	3.7
Total	137	100.0

Source: Analysis of study data using Excel

A large proportion of doctors (96.3%) reported that they corrected the cause if identifiable. Two doctors who had previously reported that they would attempt to identify the cause of an INR>4.0 now reported that they would not correct the cause if the INR was less than 6.0, no bleeding was obvious and the patient was stable or it was dependent on what the cause was. Eight doctors initially reported that they would not attempt to identify the cause of an INR>4.0; now, however, reported that they would correct the cause. Of those eight doctors, five did not clarify further, one doctor reported that the most common cause was the wrong dose taken by the patient, another reported looking for the cause only if the INR was high, for example, 7.5, and the remaining doctor said the cause would be corrected if one was looked for.

Table 4.59: Proportion of doctors who consider an increased INR above 4.0 to be an acceptable occurrence during warfarin therapy (n=142)

	Doctors	%
Yes	53	37.3
No	89	62.7
Total	142	100.0

Source: Analysis of study data using Excel and CONFINT version 4.0

Of the proportion of doctors (37.3%, 95% CI 29.3-45.8) who reported that they did find an INR>4.0 to be acceptable during warfarin therapy, 69.8% (95% CI 55.6-81.6) of those doctors clarified their answers further. Eight doctors reported that an INR>4.0 was inevitable but not desirable; nine reported that it depended on what the INR target range was set at, that is, some patients with a heart valve had a target range above 4.0; and five doctors reported that if it occurred only once, it was acceptable but required action if persistent. Three doctors reported that it should be closely monitored and acted upon, two reported that it depended on how much above 4.0 the INR was, two reported that it was acceptable only for short durations but must be corrected, and a further four doctors reported if the occurrence was only occasional and again treatment was instigated. The remaining four doctors made varying comments on an INR>4.0. One doctor said that if the occurrence of an INR>4.0 was frequent. it would influence the risk:benefit ratio and the question of whether the warfarin would be continued or not should be raised. Another doctor said it was acceptable only if the patient was asymptomatic and the high INR was detected early. The third doctor said that if the INR was known to fluctuate, it was

acceptable and the fourth doctor said that as long as the INR came down to the set target range, it was acceptable.

Table 4.60: Proportion of doctors who, if patient had an INR>4.0, would consider lowering the target range (n=142)

	Doctors	%
Yes	61	42.9
No	81	57.1
Total	142	100.0

Source: Analysis of study data using Excel

A relatively large proportion (42.9%) of doctors reported that they would consider lowering the target range if the patient had an INR>4.0. Of those doctors who reported that they would not lower the target range and made further comments, several reported that it was better to manage the INR>4.0 by adjusting the dose, increasing the frequency of monitoring, identifying the cause and discussing potential education issues with the patient.

Table 4.61: Proportion of doctors who, if INR was above target range, would adjust the dose (n=144)

	Doctors	%
Yes	141	98.6
No	3	1.4
Total	143	100.0

Source: Analysis of study data using Excel and CONFINT version 4.0

A high proportion (98.6%, 95% CI 95.0-99.8) of doctors reported that they would adjust the dose if the INR was above the target range. Those doctors who reported that they would not adjust the dose reported that they would investigate the cause and if only slightly above the target, would suggest missing a dose or two only.

Table 4.62: Proportion of doctors who ordered baseline blood tests prior to commencement of warfarin therapy (n=143)

	Doctors	%
Yes	113	79.0
No	30	21.0
Total	143	100.0

Source: Analysis of study data using Excel

A total of 71.4% of GPs reported that they would order baseline blood tests, while 95.6% of hospital-based doctors reported that they would order baseline tests. Of those GPs who reported that they would not order blood tests, six reported that they thought that baseline bloods were attended to in hospital/elsewhere, two reported that they do not initiate patients on warfarin and one doctor said that if the patient had cardiac issues, then bloods would be taken.

Table 4.63: Baseline blood tests taken (n=113)

Blood tests	Number	%
Coagulation studies	90	26.5
Liver function tests	90	26.5
Full blood count	88	25.9
Urea/Electrolytes	45	13.3
Other	26	7.8
Total	339	100.0

Source: Analysis of study data using Excel

The most common baseline blood tests ordered by doctors prior to commencement of warfarin therapy were liver function tests, coagulation studies and a full blood count. Only six doctors ordered thyroid function tests, while five ordered renal function tests. Other less common blood tests ordered included albumin, protein C and S, factor V, thrombolytic screen, lipids, blood group, ESR and iron studies.

Table 4.64: Proportion of doctors who, if dose adjustment is required, would increase the frequency of INR monitoring for a time after (n=145)

	Doctors	%
Yes	143	98.6
No	2	1.4
Total	145	100.0

Source: Analysis of study data using Excel and CONFINT version 4.0

The vast majority of doctors (98.6%, 95% CI 95.1-99.8) reported that they would increase the frequency of monitoring after dose adjustment was required. Of the two doctors who reported that they would not increase monitoring, one reported that in the hospital setting INR monitoring was daily until therapeutic anyway and the remaining doctor reported that it depended on absolute deviation from the range and rate of elevation as well as past history of response to dose alterations.

Table 4.65: Proportion of doctors who, if there is a change in the patient's health, lifestyle or medications, would increase the frequency of INR monitoring for a time after (n=143)

	Doctors	%
Yes	134	93.7
No	9	6.3
Total	143	100.0

Source: Analysis of study data using Excel and CONFINT version 4.0

Table 4.65 shows that the vast majority of doctors (93.7%, 95% CI 88.3-97.0) would increase the frequency of INR monitoring if there was a change in the patient's health. Of the nine doctors who reported that they would not increase monitoring of the INR, two were situated in the hospital setting where INR monitoring was already daily, two made no clarification, one reported that it was time consuming and impractical to do with only marginal benefits, while one doctor reported that INR monitoring would be increased only if the change was likely to have an effect on the INR and the remaining doctors reported that it was situation dependent. The doctors who reported that they would increase the monitoring if there was a change in the patient's health, lifestyle or medications, reported that especially a change in the patient's medications would prompt

an increase in the frequency of monitoring, particularly if the medication was known to cause interactions with warfarin.

Method by which patient was informed of warfarin dose and by whom, in GP rooms (n=98)

Eighty-six doctors reported the method by which their patient was informed of their warfarin dose. There were 74 (86.0%) doctors who reported that the patient was informed via telephone, while 12 (14.0%) reported that their patient was informed while in the surgery. The vast majority of doctors reported informing the patient of their warfarin dose personally themselves, especially if the patient was a high-risk patient, an INR was outside the target range or if a change in dosage was required. Approximately one third of patients were informed of their dose of warfarin by either the reception staff or nursing staff via written instructions from the doctor, especially if the patients were considered either low risk or no change in dosage was required, or it was difficult to gain contact with the patient.

Education regarding warfarin therapy the patient received that the doctor was aware of (n=142)

A total of 142 doctors thought that patients received some degree of education in some form, if not from them directly, then from another source. Hospital-based doctors reported that they thought that the majority of education came from the hospital pharmacist and that the patient received an information booklet which provided basic information and an area to record INR results and dosages. A small number of doctors reported that they provided some education to patients verbally themselves, a smaller number reported that they thought nursing staff and Hospital at Home Services nurses provided information, while three doctors were not sure what information was provided or by whom.

It is pertinent to point out that not all doctors mentioned what information was discussed with patients and reported only how the information was delivered. Thus, the topics listed below are by no means exclusive or comprehensive. However, the information that was provided does offer some insight into current trends regarding the education of patients. The information that was provided to the patient verbally by the doctors reportedly

covered such topics as the importance of INR monitoring as the most commonly discussed topic by hospital-based doctors, followed by the risks/benefits of warfarin, medication interactions, the side effects of warfarin and the signs and symptoms of bleeding to watch for, dietary aspects, indications for warfarin therapy, and the mechanisms of warfarin; in addition, one doctor discussed medic alert bracelets.

The majority of GPs reported having verbal discussions with their patients and most provided either a warfarin booklet or pamphlet. While several doctors assumed that the patient received information while an in-patient in the hospital, many reported discussing aspects of treatment throughout the course of therapy. Several GPs also referred patients to the pharmacist in the community, a very small number of GPs referred the patient to home medication review from time to time, and two GPs referred the patient to the internet to obtain warfarin information.

The topics reported as the most commonly discussed by GPs included medication interactions, dietary aspects including alcohol consumption, the importance of regular INR tests and obtaining results, the risk:benefit ratio, bleeding complications, the importance of strict compliance, the indication for warfarin and the duration of therapy. Less common topics discussed included signs and symptoms of bleeding to report, importance of informing other doctors/health care providers, set target range, the importance of recording results, reporting acute illnesses and the availability of medic alert bracelets.

Proportion of doctors who commonly discuss following lifestyle factors with patient

Table 4.66: Consistency of dietary intake of vitamin K (n=144)

	Doctors	%
Yes	90	62.5
No	54	37.5
Total	144	100.0

Source: Analysis of study data using Excel

Table 4.67: Minimising alcohol intake (n=144)

	Doctors	%
Yes	95	65.9
No	49	34.1
Total	144	100.0

Source: Analysis of study data using Excel

Table 4.68: Avoidance of binge drinking (n=144)

	Doctors	%
Yes	100	69.4
No	44	30.6
Total	144	100.0

Source: Analysis of study data using Excel

Table 4.69: Reduction of activities with considerable risk of injury, including risk of falls, in the elderly population (n=144)

	Doctors	%
Yes	102	70.8
No	42	29.2
Total	144	100.0

Source: Analysis of study data using Excel

Table 4.70: Reporting of acute illnesses to the doctor (n=143)

	Doctors	%
Yes	105	73.4
No	38	26.6
Total	143	100.0

Source: Analysis of study data using Excel

Table 4.71: Reporting any new medications and over the counter/alternative medications to their doctor (n=143)

	Doctors	%
Yes	133	93.0
No	10	7.0
Total	143	100.0

Source: Analysis of study data using Excel

As shown in Table 4.71, the vast majority of doctors (93.0%, 95% CI 87.5-96.5) reportedly discussed with their patients the importance of reporting new medications to their doctor, while approximately only two thirds of doctors reported discussing the remainder of the lifestyle factors with their patients.

4.3 Inferential statistics

Prior to inferential analysis of the data, a spreadsheet was created and the following information entered: First, the survival time of patients, that is, for those patients who had incurred at least one episode of over-anticoagulation, the number of days from initiation of warfarin therapy to the time of the first episode of over-anticoagulation, and for those patients who had not incurred any episode of over-anticoagulation, the number of days from initiation of warfarin to the time the warfarin was ceased or to the end of the five-months study period. Second, dichotomous data for those patients who had incurred at least one episode of over-anticoagulation as opposed to those patients who had not incurred any episodes of over-anticoagulation. Third, the number of episodes of over-anticoagulation each patient incurred and the length of time each patient was on warfarin therapy in the study period of 21.8 weeks. Finally, variables that were thought to impact on episodes of over-anticoagulation were entered into the spreadsheet. Those variables included the gender and age of the patient and whether the patient had received antibiotics during the course of the study period. Any antibiotics that were prescribed to the patient were included, not just those antibiotics that are known to interact with warfarin. Dichotomous data was recorded pertaining to whether the patient was taking panadol, amiodarone, had been diagnosed with CCF, had diarrhoea for more than two days, had experienced a decreased oral intake and whether the patient had progressed through the Hospital at Home Services or not. Finally, the frequency of monitoring that occurred

during the initial month of warfarin therapy and the patient's Hb and serum albumin levels were also entered.

A formal test for normality using the Shapiro-Wilks test was applied to the covariates, age, frequency of monitoring during the initial month (first 30 days) of warfarin therapy, serum albumin and Hb prior to inferential statistics. The Shapiro-Wilks test is the standard formal test for normality and is usually applied when the sample is of a small to median size, that is, n=10-2000. The W statistic is the correlation between the given data and their corresponding normal scores and thus, when W=1, the data are said to be perfectly normal in distribution. When W is significantly smaller than one the assumption of normality is not met (Garson 2007b).

Survival analysis using the proportional hazards regression model (Cox Model) without time-dependent covariates was then applied to the data, using SPSS version 15.0. According to Ryan (2002:2), a leading statistician, survival analysis techniques are utilised when the principal endpoint of a study is the time until a specified event has occurred and can provide information such as 'the average (average or mean) survival time', 'the probability of surviving to a specified time', 'whether one treatment favourably alters the survival experience of patients compared to a second (third, etc.) treatment' or 'whether an apparent difference in survival attributed to a factor (e.g. a course of chemotherapy) remains after controlling for other factors'. As Ryan (2002) notes, the endpoint of interest need not necessarily be that of death, but may be of time to resolution of a symptom, recurrence of a tumour or days spent in intensive care. In this study, the endpoint of interest was time to an episode of over-anticoagulation.

According to Klein and Moeschberger (1997), a frequently encountered problem in analysing survival data pertains to the lack of ability of the model to account for concomitant information, that is, covariates or independent variables. Thus, Cox in 1972, proposed a method for modelling the hazard function on one or more covariates (Ryan 2002). The proportional hazards model (Cox Regression model) is not based on any assumptions concerning the nature or shape of the underlying survival distribution and assumes that the underlying hazard rate is a function of the independent variables (covariates), that is, no assumptions are made about the nature or shape of the hazard function and as such may be considered to be a nonparametric method (StatSoft Inc 2003).

The Cox Regression output statistic indicates the regression coefficient (B) in the unstandardised form, the standard error around the coefficient for the constant (SE), its Wald test significance value (Wald), the degrees of freedom (df) and the significance value of the coefficient (Sig.). If the Sig.>0.05, the covariate effect cannot be assumed to be different from zero, that is, if Sig.<0.05 it can be concluded that the variable is useful in the model (Garson 2007a). There is only one degree of freedom because there is only one predictor in the model, that is, the constant (UCLA Academic Technology Services accessed 23 July 2007).

In an email communication on 23 July 2007, a reputable statistician assisting with the statistical analysis of this study pointed out that for a log binomial generalised linear model, Exp(B) is the Relative Risk (A. Esterman 2007, pers. comm., 23 July). The Relative Risk, shown as Exp(B), indicates that when the relative risk is 1.0, the characteristic has no influence on the event, but when the Relative Risk exceeds 1.0, the probability of an event increases (Garson 2007a).

An Omnibus Test of Model Coefficients was applied to the frequency of monitoring during the initial month of therapy data to assess the predictive ability of the covariate in the model. In an email communication on 23 July2007, the statistician advised that the Omnibus Test of Model Coefficients is a measure of goodness of fit, and it compares the current model with a model without any predictors (A. Esterman 2007, pers. comm., 23 July). If the Sig.>0.05, then the effect of the covariate cannot be assumed to be different from zero (Garson 2007a).

Finally, a Poisson model was applied using Stata version 7.0. The Poisson distribution provides a model for the random occurrence of observed events that are rare; there may be intervals when no event actually occurs, in a short interval of time. Thus, it can predict the probability of specific divergences from that rate (Brooks 2001).

The Z and the P>[z] are the test statistic and the p-value respectively of the null hypothesis that an individual predictor's regression coefficient is equal to zero given that the rest of the predictors are in the model. The Z= the ratio of the coefficient to the Standard Error of the respective predictor and it follows a standard normal distribution (UCLA Academic Technology Services accessed 24 July 2007).

The Std. Err (standard error) of the individual regression coefficients are used in the calculation of the Z test statistic and the confidence interval of the regression coefficient.

The IRR or the incidence rate ratio is the rate at which events occur and are obtained by exponentiating the Poisson regression coefficient. The 95% conf. interval states that the researcher is 95% confident that upon repeated trials, 95% of the CI's would include the population incidence rate ratio, given that the other covariates are in the model (UCLA Academic Technology Services accessed 24 July 2007).

4.4 Research Question: Are episodes of over-anticoagulation potentially preventable or unforeseeable?

4.4.1 Quantification of gender as predictor of an episode of over-anticoagulation

Table 4.72: Cox Regression for gender

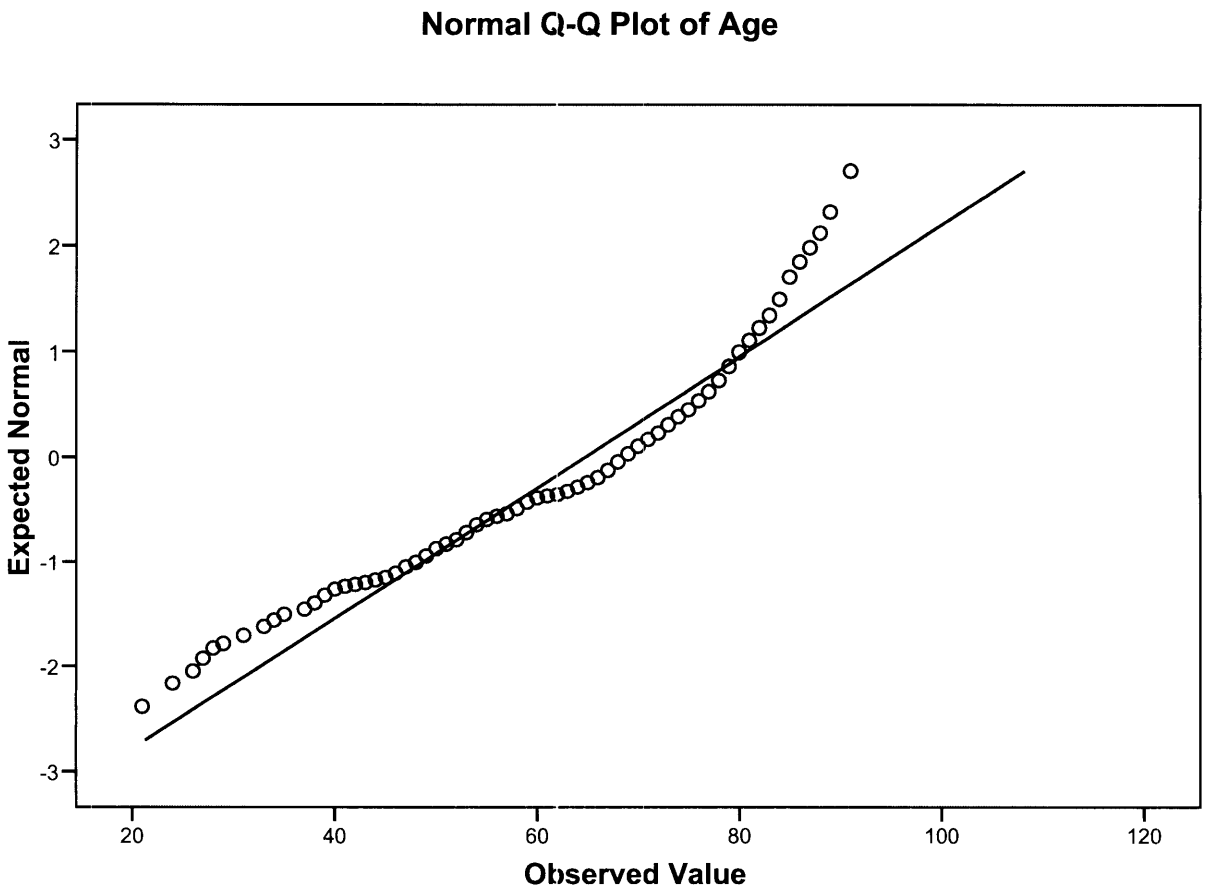
B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
						Lower	Upper
.082	.192	.184	1	.668	1.086	.746	1.581

Source: Analysis of study data using SPSS version 15.0

Survival analysis using a Cox Regression model was utilised, using SPSS version 15.0, to quantify the effect of gender as a predictor of an episode of over-anticoagulation. The dependent variable was an episode of over-anticoagulation and the independent variable was gender. Results indicated that gender as a predictor of an event, that is, an episode of over-anticoagulation, was not a significant factor (Sig.=0.668) in this study.

The Poisson model, using Stata version 7.0, was then applied to estimate the incidence rate ratio of episodes of over-anticoagulation using gender as a covariate. Results indicated that gender was not significant (Z=1.66; P>[z]=0.097; IRR=1.29; Standard Error=0.203; (95% CI .953-1.76) as P>[z] is greater than 0.05).

4.4.2 Quantification of age as predictor of an episode of over-anticoagulation



Graph 4.13: Quantile-by-Quantile plot for age

Source: Analysis of study data using SPSS version 15.0

The Quantile-by-Quantile (Q-Q plot), as shown in Graph 4.13, was applied, using SPSS version 15.0, to graphically evaluate normality prior to the application of the Cox Regression model and the Poisson model. According to Garson (2007), the Q-Q plot marks the quantiles of a covariate's distribution against the quantiles of the test distribution resulting in the formation of a 45-degree line when the observed values have conformed with the hypothetical distribution. As indicated in the above graph, the deviations were slightly skewed, thus it would be reasonable to assume that the distribution of age in the patients was minimally negatively skewed.

Ryan (2002) states that the coefficient of skewness should equal zero and the coefficient of kurtosis should equal three for a normal distribution. Results of a test for skewness and

kurtosis of data for age, using Stata version 7.0, were skewness=-0.7718 and kurtosis=2.8510, indicating the data were slightly skewed with minimal kurtosis.

The Shapiro-Wilks test was then performed to formally assess normality of the data, using Stata version 7.0. Results indicated that the distribution was relatively normal as the W=0.9386.

Table 4.73: Cox Regression for age

B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
						Lower	Upper
.024	.007	12.998	1	.000	1.024	1.011	1.038

Source: Analysis of study data using SPSS version 15.0

Survival analysis using a Cox Regression model was utilised, using SPSS version 15.0, to quantify the effect of age as a predictor of an episode of over-anticoagulation. Results indicated that age was a strong predictor of an episode of over-anticoagulation occurring as Sig.=0.000. These results indicate that for each year of age a patient is 1.02 times more likely to incur an episode of over-anticoagulation during warfarin therapy.

The Poisson model, using Stata version 7.0, was then applied to the data to estimate the incidence rate ratio for the number of episodes of over-anticoagulation where the covariate was age. Results confirmed that age was a significant factor: Z=2.84; P>[z]=0.005; IRR=1.01; Standard Error=0.005; (95% CI 1.00-1.02). For each one-year increase in age, the incidence rate ratio for episodes of over-anticoagulation would be expected to increase by 1.01, while all other variables in the model are held constant.

4.4.3 Quantification of antibiotics as a predictor of an episode of over-anticoagulation

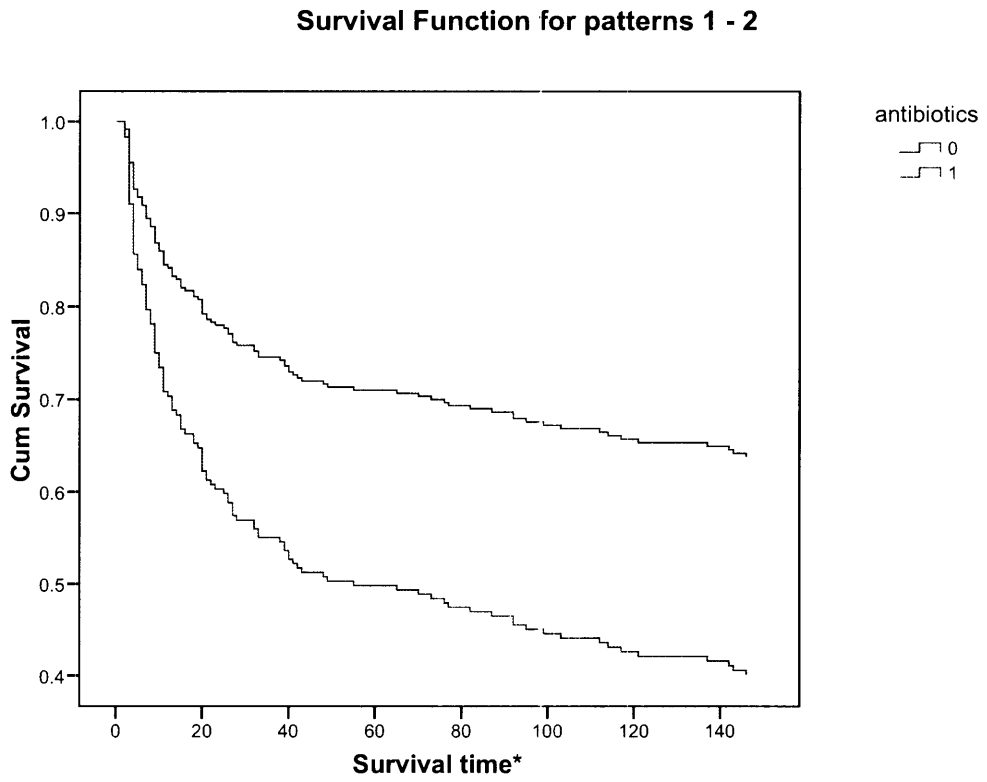
Table 4.74: Cox Regression for antibiotics

B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
						Lower	Upper
.710	.201	12.518	1	.000	2.033	1.372	3.012

Source: Analysis of study data using SPSS version 15.0

Survival analysis using the Cox Regression model was utilised, using SPSS version 15.0, to quantify the effect of antibiotics as a predictor of an episode of over-anticoagulation. Results indicated that, as a predictor of an episode of over-anticoagulation occurring, antibiotics, as a variable, is highly significant as Sig.=0.000. Thus, a patient receiving antibiotics when on warfarin therapy is 2.03 times more likely to incur an episode of over-anticoagulation. It is important to note that all antibiotics taken by patients were included in the data and not only those known to impact on the effect of the INR results.

When the Poisson model was applied to the data, using Stata version 7.0, the results indicated that antibiotics were highly significant (P>[z]=0.000) and that if the patient was receiving antibiotics while receiving warfarin, his/her incidence rate ratio for an episode of over-anticoagulation would be expected to increase by 1.81, while holding all other variables in the model constant. Results were as follows: Z=3.80; P>[z]=0.000; IRR=1.81; Standard Error=0.286; (95% CI 1.33-2.47).



Graph 4.14: Survival plot for antibiotics

Source: Analysis of study data using SPSS version 15.0

Graph 4.14 shows clearly that the time to an event, that is, an episode of over-anticoagulation, is much shorter if a patient is prescribed antibiotics concomitantly with warfarin.

4.4.4 Quantification of paracetamol as a predictor of an episode of over-anticoagulation

Table 4.75: Cox Regression for Paracetamol

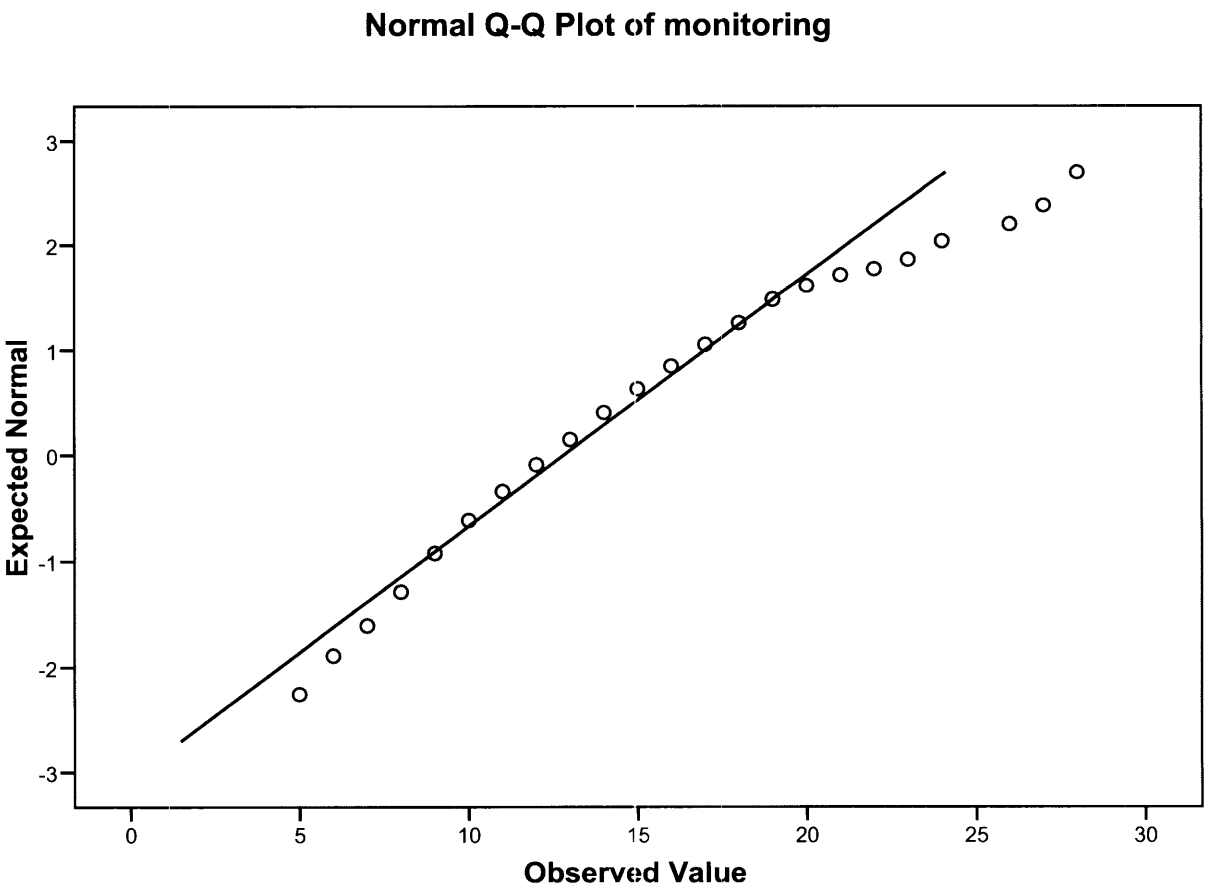
B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
						Lower	Upper
.437	.204	4.593	1	.032	1.548	1.038	2.307

Source: Analysis of study data using SPSS version 15.0

Survival analysis using a Cox Regression model was utilised, using SPSS version 15.0, to quantify the effect of paracetamol as a predictor of an episode of over-anticoagulation. Results indicated that paracetamol was only a marginal predictor of an episode of over-anticoagulation with Sig.=0.032.

When the Poisson model was applied, using Stata version 7.0, results indicated that paracetamol was a significant factor: Z=2.84: P>[z]=0.005: IRR=1.57: Standard Error=0.254; (95% CI 1.15-2.16). These results indicate that a patient taking paracetamol while receiving warfarin therapy would expect his/her incidence rate ratio for an episode of over-anticoagulation to increase by 1.57, while holding all other variables in the model constant.

4.4.5 Quantification of frequency of monitoring during initial month (first 30 days) of treatment as predictor of an episode of over-anticoagulation



Graph 4.15: Quantile-by-Quantile plot for frequency of monitoring during initial month (30 days) of warfarin therapy

Source: Analysis of study data using SPSS version 15.0

When a Q-Q plot was applied to the data, as shown in Table 4.15, deviations from the normal 45-degree line of the test distribution were relatively small. A test for kurtosis=4.0704 and skewness=0.7906, using Stata version 7.0, indicated that the data were slightly but not significantly distorted. The W statistic for the Shapiro-Wilks test for normality, using Stata version 7.0, was 0.9879, indicating that the assumption of normality was met.

Table 4.76: Cox Regression for frequency of monitoring during the initial month (30 days) of warfarin treatment

B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
						Lower	Upper
0.094	0.020	22.456	1	0.000	1.098	1.057	1.142

Source: Analysis of study data using SPSS version 15.0

Survival analysis using the Cox Regression model was applied to the data and results indicated that the frequency of monitoring during the initial month of treatment, as a predictive variable for an episode of over-anticoagulation, was a very significant factor as Sig.=0.000. These results indicate that a patient is likely to incur an episode of over-anticoagulation 1.098 times more often if frequency of monitoring is decreased. The Omnibus test of the Model Coefficient results indicated that the null hypothesis was a good fit as Sig.=0.000; df=1; Chi-square=22.485.

The Poisson model was applied to the data, using Stata version 7.0. Results indicated that the frequency of monitoring during the initial month of treatment was a very significant factor: Z=5.08; P>[z]=0.000; IRR=1.08; Standard Error=0.0164; (95% CI 1.04-1.11). These results indicate 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.

4.4.6 Quantification of amiodarone as predictor of an episode of over-anticoagulation

Table 4.77: Cox Regression for amiodarone

B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
						Lower	Upper
.717	.237	9.127	1	.003	2.049	1.287	3.263

Source: Analysis of study data using SPSS version 15.0

Survival analysis using a Cox Regression model was utilised, using SPSS version 15.0, to quantify the effect of amiodarone as a predictor of an episode of over-anticoagulation.

Results indicated that amiodarone was a strong predictor of an event occurring since Sig.=0.003. These results indicate that a patient taking amiodarone and warfarin concomitantly is 2.049 times more likely to incur an episode of over-anticoagulation.

When the Poisson model was applied, using Stata version 7.0, to estimate the incidence rate ratio for an episode of anticoagulation in a patient taking amiodarone while receiving warfarin, results indicated that amiodarone was a significant factor: Z=4.41; P>[z]=0.000; IRR=2.21; Standard Error=0.399; (95% CI 1.55-3.15). These results show that if a patient were receiving amiodarone and warfarin concomitantly, the incidence rate ratio for an episode of over-anticoagulation would be expected to increase by 2.21, while holding all other variables in the model constant.

4.4.7 Quantification of Congestive Cardiac Failure (CCF) as predictor of an episode of over-anticoagulation

Table 4.78: Cox Regression for CCF

B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
						Lower	Upper
.612	.208	8.676	1	.003	1.845	1.227	2.773

Source: Analysis of study data using SPSS version15 0

When survival analysis using a Cox Regression model was applied to quantify the effect of CCF as a predictor of an episode of over-anticoagulation occurring, results indicated that it was significant (Sig.=0.003). Therefore, a patient experiencing CCF while receiving warfarin therapy was 1.845 times more likely to incur an episode of over-anticoagulation.

The Poisson model was applied, using Stata version 7.0, to estimate the incidence rate ratio for an episode of over-anticoagulation in a patient who had been diagnosed with CCF and taking warfarin therapy. The results indicated that the incidence rate ratio for an episode of over-anticoagulation would be expected to increase 1.93 times when a patient has CCF, if all other variables in the model were constant. Results were as follows: Z=4.15; P>[z]=0.000; IRR=1.93; Standard Error=0.309; (95% CI 1.41-2.64).

4.4.8 Quantification of diarrhoea as a predictor of an episode of over-anticoagulation

Table 4.79: Cox Regression for diarrhoea for at least two consecutive days

B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
						Lower	Upper
1.512	.287	27.686	1	.000	4.538	2.583	7.971

Source: Analysis of study data using SPSS version 15.0

Survival analysis using a Cox Regression model was utilised to quantify the effect of diarrhoea as a predictor of an episode of over-anticoagulation. Results indicated that diarrhoea for at least two consecutive days was a strong predictor of an event occurring (Sig.=0.000). These results suggest that a patient experiencing diarrhoea for at least two consecutive days while receiving warfarin therapy is 4.538 times more likely to incur an episode of over-anticoagulation.

The estimated incidence rate ratio of a patient incurring an episode of over-anticoagulation when experiencing diarrhoea for at least two consecutive days while receiving warfarin, using the Poisson model with Stata version 7.0, was 3.69, while holding the other variables constant in the model. This is a highly significant factor. Results were as follows: Z=6.46; P>[z]=0.000; IRR=3.69; Standard Error=0.747; (95% CI 2.48-5.49).

4.4.9 Quantification of decreased oral intake as predictor of an episode of over-anticoagulation

Table 4.80: Cox Regression for Decreased Oral Intake

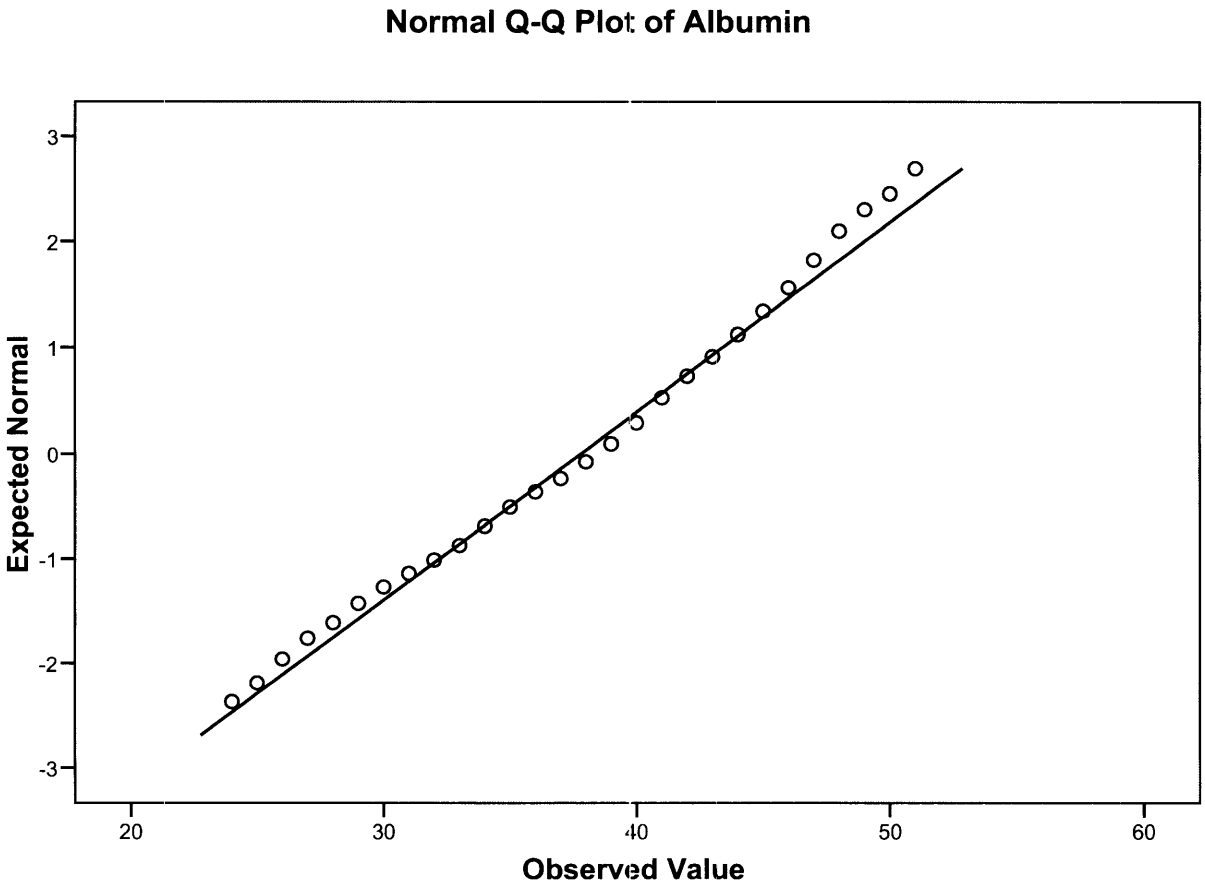
B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
						Lower	Upper
1.782	.219	66.064	1	.000	5.944	3.867	9.135

Source: Analysis of study data using SPSS version 15.0

After a Cox Regression model was utilised, using SPSS version 15.0, to quantify the effect of decreased oral intake as a predictor of an episode of over-anticoagulation, results indicated that decreased oral intake was a strong significant factor at Sig.=0.000. If a patient is experiencing a decreased oral intake while taking warfarin, he/she is almost six times more likely to incur an episode of over-anticoagulation.

The Poisson model, using Stata version 7.0, was applied to the data to estimate the rate ratio for an episode of over-anticoagulation in a patient suffering a decreased oral intake while receiving warfarin therapy. Results indicated that a decreased oral intake was a significant factor (Z=7.62; P>[z]=0.000; IRR=3.50; Standard Error=0.577; (95% CI 2.53-4.84), revealing that if a patient experienced a decreased oral intake while receiving warfarin, he/she could expect the incidence rate ratio for an episode of over-anticoagulation to increase by 3.50, while holding all other variables in the model constant.

4.4.10 Quantification of decreased albumin as predictor of an episode of over-anticoagulation



Graph 4.16: Quantile-by-Quantile plot for serum albumin

Source: Analysis of study data using SPSS version 15.0

Graph 4.16 shows that the Q-Q plot applied to the data to observe whether values are in conformity with the hypothetical distribution indicates that deviations from the 45-degree line are not significant. This indicates that serum albumin was normal in distribution.

When the formal test of normality, the Shapiro-Wilks test, was applied, using Stata version 7.0, results indicated that the data were normally distributed (W=0.9879). Results for a test of skewness=-0.4094 and kurtosis=3.0370, using Stata version 7.0, indicated that the data were normally distributed.

Table 4.81: Cox Regression for decreased albumin

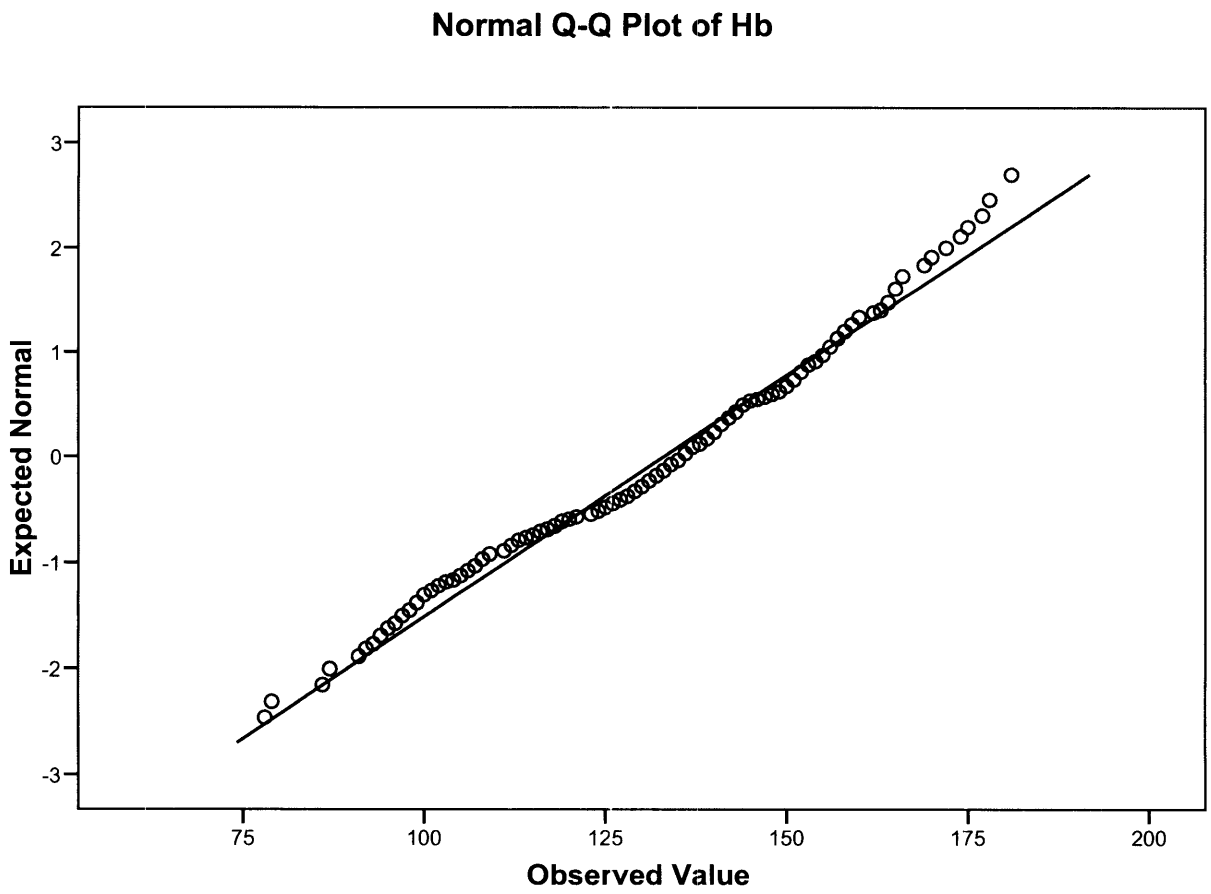
B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
						Lower	Upper
-.051	.017	9.168	1	.002	.950	.919	.982

Source: Analysis of study data using SPSS version 15.0

Survival analysis using a Cox Regression model was utilised to quantify the effect of low albumin as a predictor of an episode of over-anticoagulation. Results indicated that a normal albumin level is a protector against an episode of over-anticoagulation, since Sig.=0.002, Exp(B)=0.950.

When the incidence rate ratio for an episode of over-anticoagulation in a patient with a low albumin (<31 g/L) taking warfarin was estimated, results from the Poisson model, using Stata version 7.0, revealed that there was a decrease in the incidence rate ratio when the serum albumin was within normal limits. Results were as follows: Z=-4.89; P>[z]=0.000; IRR=-.941; Standard Error=0.011; (95% CI 0.918-0.964).

4.4.11 Quantification of decreased haemoglobin level (Hb) as a predictor of an episode of over-anticoagulation



Graph 4.17: Quantile-by-Quantile plot for haemoglobin level (Hb)

Source: Analysis of study data using SPSS version 15.0

The quantiles of the variable's distribution, that is, haemoglobin levels, plotted against the quantiles of the test distribution, as shown in Graph 4.17, indicate that there is no significant deviation from the 45-degree line. These results indicate that the observed values are in conformity with the hypothetical distribution.

A test for skewness=-0.3179 and kurtosis=2 4915 was applied, using Stata version 7.0, indicating results were reasonably within normal limits. The results of the Shapiro-Wilks test for normality, using Stata version 7.0, indicate that the distribution was also within normal limits since W=0.9823.

Table 4.82: Cox Regression for decreased Hb

B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
						Lower	Upper
-.008	.004	3.227	1	.072	.992	.984	1.001

Source: Analysis of study data using SPSS version 15.0

When a Cox Regression model was utilised to quantify the effect of a decreased Hb as a predictor of an episode of over-anticoagulation, the results indicated that there was no significance (Sig.=0.072).

The Poisson model, using Stata version 7.0, was applied to the data to estimate the incidence rate ratio for an episode of over-anticoagulation in a patient with a decreased Hb (<100 g/L) while taking warfarin therapy. Results were as follows: Z=-3.00; P>[z]=0.003; IRR=0.990; Standard Error=0.003; (95% CI 0.983-0.996), indicating that there was no expected increased in the incidence rate ratio if the Hb was within normal limits.

4.4.12 Quantification of Hospital at Home Services as predictor of an episode of over-anticoagulation

Table 4.83: Cox Regression for the Hospital at Home Services

B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
						Lower	Upper
-.409	.194	4.450	1	.035	.664	.454	.971

Source: Analysis of study data using SPSS version 15.0

A Cox Regression model was utilised to quantify the effect of Hospital at Home Services as a predictor of an episode of over-anticoagulation. Results indicated that it was marginally significant only (Sig.=0.035).

The Poisson model, using Stata version 7.0, was applied to the data to estimate the incidence rate ratio for an episode of over-anticoagulation in a patient who had progressed through the Hospital at Home Services while being commenced on warfarin

therapy. The results indicated that the covariate was significant with no expected increase in the incidence rate ratio if all other variables in the model were kept constant: Z=-3.22; P>[z]=0.001; IRR=0.612; Standard Error=0.093; (95% CI 0.454-0.825). That is, if patients attended the Hospital at Home Services, the incidence rate ratio could be expected to fall, while holding all other variables in the model constant.

4.4.13 Best predictive model for number of episodes of over-anticoagulation

Table 4.84: Poisson analysis for best predictive model for incidence rate ratios for an episode of over-anticoagulation

	IRR	Std. Err.	z	P>[z]	[95% Conf. Interval	
Monitoring	1.066	0.017	3.95	0.000	1.033	1.101
Hospital at Home	0.578	0.090	-3.48	0.000	0.424	0.787
Decreased oral intake	2.523	0.442	5.27	0.000	1.788	3.559
Albumin	0.956	0.012	-3.46	0.001	0.932	0.980

Source: analysis of data using Stata version 7.0

Each significant covariate was added to the model, using Stata version 7.0, to determine the best predictive model for the incidence rate ratios for an episode of over-anticoagulation. When different combinations of the variables were added to the model, the significance of some of the covariates overall were radically reduced, indicating that, as expected, many of the covariates were significantly interrelated. According to the statistician, 'if two predictor variables are both significantly related to an outcome measure, and they overlap in the information they contain, if you put them both into a model, the chances are that one or both will no longer be significantly related to the outcome measure' (A. Esterman 2007, pers. comm., 23 July).

Final findings indicated that the frequency of monitoring during the initial month of treatment, decreased oral intake, serum albumin levels and the Hospital at Home Services were the most significant covariates for the best predictive model to estimate the incidence rate ratios for an episode of over-anticoagulation. When added to the model, the findings revealed that the Hospital at Home Services (P>[z]=0.000; IRR=0.578) and albumin levels (P>[z]=0.001; IRR=0.956) within normal limits act as protective factors

against an episode of over-anticoagulation, while a decreased frequency of INR monitoring during the initial month of treatment (P>[z]=0.000) and a decreased oral intake (P>[z]=0.000) remain strongly significant factors that could expect to increase the incidence rate ratio of episodes of over-anticoagulation by 1.066 and 2.523 times respectively.

4.5 Conclusion

In summary, this chapter has provided the justification for the data analysis techniques used, a summary of the data and the findings of the study. Descriptive statistics were used to summarise and describe the data collected and inferential statistics were used to answer the research question.

First, the demographic characteristics of the patients were documented. Second, descriptive statistics provided a profile of the sample in order to address the five objectives of the study. Finally, inferential statistics, using the Cox Regression model and the Poisson distribution, were used to address the research question.

The following chapter will provide a discussion of the major conclusions and findings of this study and the implications of those findings for policy and practice.