SUPPLEMENTATION TO IMPROVE ANTICOAGULATION CONTROL WITH LOW DOSE VITAMIN K AS AN ADJUVANT TO WARFARIN THERAPY: A DOUBLE BLIND, PLACEBO-CONTROLLED RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Vitamin K Antagonists [VKA] are the most frequently used oral anticoagulants in clinical practice; however, many patients fail to achieve adequate anticoagulation control. We conducted a randomized, placebo controlled, double blind study of Vitamin K1 (200mcg per day, Swanson™ Vitamins) in a population with predominantly venous thromboembolism aimed at evaluating its effectiveness in improving anticoagulation control in unstable patients. This study also aimed to evaluate the impact that clinical variables, patient anticoagulation knowledge, and genetic polymorphisms in genes known to impact warfarin and Vitamin K metabolism [VKORC1, CYP4F2, CYP2C9] had on anticoagulation control and intervention effectiveness. A total of N=54 patients were enrolled in the study over 15 months [January 2009 to June 2010]. Change score analysis and multivariate linear regression modelling of anticoagulation control measures were performed. No statistically significant reduction was observed in the Vitamin K1 arm for percent time in therapeutic range; however, reduction was observed in standard deviation of INRs [Change Score Vitamin K = -0.259, p=0.0261; Regression Model 95% C.I Beta Vitamin K = -0.38 to -0.08] during the intervention period. Adjusting for treatment group allocation, independent predictors of increased INR standard deviation included: ≥5 alcoholic drinks per week [95% C.I Beta = 0.04 to 0.41], self-reported dosing errors [95% C.I Beta = 0.13 to 0.47], and missed INR appointments [95% C.I Beta = 0.002 to 0.05]

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1. INTRODUCTION

Vitamin K Antagonists [VKAs] such as warfarin [Coumadin™], acenocoumarol [Sintrom™], and phenprocoumon [Marcoumar™] are the current global standard for oral anticoagulation therapy in the treatment and/or prophylaxis of venous thrombosis, atrial fibrillation, pulmonary embolism, and acute myocardial infarction[1] .

Vitamin K antagonists operate by interfering with the normal coagulation cascade. During the coagulation cascade, the procoagulant factors II, VII, IX, and X undergo carboxylation of their N-terminal glutamate residues to become functional. Vitamin K is an essential cofactor for this carboxylation reaction along with the C1 subunit of the enzyme Vitamin K Epoxide Reductase [VKORC1]. During this enzymatic process Vitamin K loses electrons and goes from its reduced state to its oxidized state. The Vitamin K is then regenerated by the VKOR enzyme to allow for continued carboxylation of other procoagulant cofactors. VKAs inhibit the activity of the VKOR enzyme thereby inhibiting the regeneration of Vitamin K and consequently producing undercarboxylated clotting factors with reduced procoagulant activity[2, 3]. In addition to its role in the coagulation cascade, Vitamin K also plays a role as a cofactor in the carboxylation of oseteocalcin and bone matrix gla protein -- both essential elements for bone turnover and vascular calcification respectively. Given the essential function of Vitamin K it is important to understand this compound and its place in our diet.

Vitamin K is a lipid soluble compound that exists in nature in two forms – Vitamin K1 [phylloquinone] and Vitamin K2 [menaquinone] produced by plants and bacteria respectively. Vitamin K1 is the primary form that humans ingest in their diet with dark green leafy vegetables having the highest quantities of the vitamin[4]. Vitamin K2, on the other hand, is notably produced by bacteria in the intestines of vertebrates. Very few foods

contain an appreciable amount of Vitamin K2, with *Natto*, a Japanese fermented soybean product being an exception. Dietary recommendations state that the recommended daily allowance for Vitamin K in humans is approximately 70mg or 1mg/kg.[2]

1.1 Measures of Anticoagulation Control

When clinically assessing the level of anticoagulation in a patient on a Vitamin K antagonist a commonly used measure is the PT [Prothrombin Time] or the more frequently used INR [International Normalized Ratio]. The INR is a standardized measure of anticoagulation that incorporates the patient's prothrombin time divided by the prothrombin time of a pooled population of non-anticoagulated patients all raised to the power of a standardization coefficient [ISI]. Hutten and colleagues[5] summarized quite thoroughly various proposed measures of anticoagulation control. A specific crude measure mentioned in the paper was the number of INR measures within target range expressed as a percentage of the total number of INRs obtained. A disadvantage of this method is that it does not incorporate time and, as stated by the authors, can not thus be used to calculate incidence rate of recurrent thromboemboli and bleeding complications at different INR levels. Measures that incorporate time include the Equidivision method[6] [proposed by Duxbury], where the change between two consecutive INR measures is assumed to have occurred halfway between the interval, and the Linear Interpolation method [also known as the Rosendaal method] wherein the INR between two measurements is assumed to vary linearly from the first INR to the second INR[7]. Hutten and colleagues[5] demonstrated that the linear interpolation method is superior to the equidivision method and equivalent to a hybrid model proposed by the authors. Upon modeling the various methods on existing trial data, Hutten and colleagues observed that the equidivision method was insensitive to variation in length of time [as the authors were able to delete up to 30% of the observations with no appreciable

change in time in therapeutic range]. However, when predicting intermediary INR results the equidivision method was inferior to both the Rosendaal and hybrid methods. Both the Rosendaal and Hybrid methods performed equally well in predicting intermediary INR results with the Hybrid method being less sensitive to variation in length of time between INR measures than the Rosendaal method. Schmitt et al[8], in a published review, also compared the advantages and disadvantages of three methods [fraction of INRs in therapeutic range, cross section of the files, and Rosendaal linear interpolation] for calculating time in therapeutic range [TTR] but did not provide any recommendations as to the superiority of one method over another. Fitzmaurice and colleagues[9] in a systematic review of 15 papers [N= 53 to 2545 patient] examining outcome measures for the therapeutic effectiveness of oral anticoagulation found that frequently used measures included : time in range [7/15 papers], mean INR [5/15 papers], proportion of tests in range [6/15 papers], and mean warfarin dose [5/15 papers]. Other reported measures of anticoagulation control in the review by Fitzmaurice and colleagues[9] included: dose changes each month, distribution of INR results, deviation of INR value from mean, percentage dose changes, time between visits, and median INR value.

Samsa and Matchar[10] in a systematic review of trials assessing patient self-management [PSM] of anticoagulation with point of care INR testing confirmed the strength of the relationship between time in therapeutic range [TTR] and clinical outcomes [bleeding and thromboembolism] thereby supporting its use as a primary outcome variable in trials. Additionally they proposed that increasing frequency of testing often seen with studies with PSM may increase TTR; however, the authors maintained that the studies were few and not definitive. The authors made recommendations for future studies including: using high quality anticoagulation as control groups, using TTR as a primary outcome measure, and

basing sample size calculations a 5-10% absolute improvement in TTR. Despite the frequent use of TTR as a surrogate outcome in clinical trials it should be noted that some authors have shown that changes in TTR are often only associated with marginal changes in clinical outcomes [bleeding and thromboembolism]. Van Walraven and colleagues[11] in a meta-analysis and Monte Carlo simulation study using data from studies reporting both surrogate and clinical outcome measures found small changes in clinical outcomes when surrogate markers changed. A mean increase in % TTR of 8.4% [Range 1.8-18%] was associated with a non-significant decrease in hemorrhagic and thrombotic events [mean 0.66% per yr; Range 0.3-1.42% per year]. It should also be noted that the lack of use of direct clinical outcome variables [hemorrhage and thrombosis] in studies may not be practical due to the potentially large sample sizes that would be required for such infrequent events.

Based on the aforementioned results and the fact that the Rosendaal method is widely used in the literature and in clinical practice at the Ottawa Hospital – the authors chose to adopt it as the primary method of determining time in therapeutic range [TTR] in order to evaluate anticoagulation control in our study.

1.2 Impact of Poor Anticoagulation Control

Prior studies have shown that up to half of patients who receive warfarin fail to stabilize within their target range[12] leading to a resultant increased risk of thromboembolism or bleeding. A systematic review by Oake et al[13] analyzing results from 71,065 patients on long term oral anticoagulant therapy found that 44% of all hemorrhages [95% C.I 39-49%] occurred when patient INRs were above target therapeutic range and 48% of all thromboemboli [95% C.I 41-55%] occurred when patient INRs were below target therapeutic range. Additionally, Butchart et al[14] in a cohort study of 1476 patients who underwent single valve replacement noted a statistically significant trend towards increasing

mortality with high anticoagulation variability [Hazard Ratio 1.8; on multivariate analysis for each 20% increase in variability]. Van Dongen et al[15] also reported that for patients who spent more than 50% of their time below target range and who had a first episode of DVT [deep vein thrombosis] were at higher risk for Post-Thrombotic Syndrome [OR 2.71 95% CI 1.44-5.10].

Given the aforementioned statistics; the development of interventions to help patients stay within their target therapeutic range would potentially contribute greatly to improved patient safety and decreased adverse events while on oral anticoagulants.

1.3 Vitamin K Supplementation to Improve Anticoagulation Control

Numerous studies summarized in the section below have attempted to evaluate factors that influence anticoagulant stability; however, a large portion of the intra-individual variability in response to warfarin is unexplained. A recently proposed hypothesis is that a patient's vitamin K status [getting a sufficient and consistent dietary intake of vitamin K] may strongly influence the stability of INRs while on oral anticoagulant therapy. Sconce and colleagues[16] demonstrated in a case control study of 42 patients that the mean daily vitamin K intake for patients with unstable anticoagulation control was 2.5 times lower than that for patients with stable control during a two week study period. Couris and colleagues[17] confirmed this result in a five week study measuring the dietary changes, warfarin dose, and INRs of 60 patients clearly demonstrating that as dietary Vitamin K intake increased, patient INRs became more stable. Conversely, they also demonstrated that as Vitamin K intake decreased the patients' INRs became more variable. Khan and colleagues[18] also supported this conclusion with an observational study that demonstrated that vitamin K intake over the previous 4 days and INR were inversely proportional for patients on stable doses of warfarin.

The authors noted that every 100mg increase in dietary vitamin K intake over 4 days resulted in a decrease in INR of 0.2.

The aforementioned findings led to a number of retrospective and prospective studies being initiated as well as two randomized, controlled trials to assess the impact of low-dose Vitamin K supplementation on improving patient stability on oral anticoagulants.

The observational studies by Reese et al[19] and Ford et al[20] utilized Vitamin K supplementation of 100 µg/day and 500µg/day respectively, and both studies found that the time patients were in therapeutic range increased and the overall variability of patient INRs decreased. Reese and colleagues[19] observed, in their retrospective case series of 8 patients; that the number of INRs within 0.2 units of the target range increased from 32% to 57% [a relative increase of 76%]. Ford et al.[20] found in a prospective cohort of 9 patients that vitamin K supplementation resulted in 56% of the patients [n=5] having decreased INR variability at 2-7 days after initiation of Vitamin K. Since Vitamin K counteracts the effect of warfarin [a vitamin K antagonist] a requisite increase in warfarin dose was required to bring back the INRs within therapeutic range, this dose increase ranged from 6-95% of the pre-intervention dose. Nevertheless, while these observational studies showed benefit there were some that did not. A case study reported by Leong[21] involving supplementation with 80µg/day of Vitamin K showed no benefit with respect to percentage of time within therapeutic range. Earl and colleagues[22] published a series of case reports assessing Vitamin K supplementation in varying doses from 100 to 300 µg/day and they found no improvement in INR stabilization and observed that increases in warfarin dose were required in most cases.

At the time of the initiation of this study, only one of the two RCTs[23, 24] to date had assessed the efficacy of low dose supplementation in unstable patients. Sconce and

colleagues[23] demonstrated that INR stability did improve with Vitamin K supplementation in a double blind study of 70 unstable warfarin patients randomized to either 150 μg/day Vitamin K or placebo. An 87% reduction in the standard deviation of patient INR values was seen relative to a 59% reduction found in the control group. In addition, the time within therapeutic range increased from 15% in the placebo group to 28% in the Vitamin K group. Just as was seen by Ford and colleagues[20], Sconce et al[23] documented that the warfarin dosage among Vitamin K supplemented patients needed to be increased in order to maintain INR values within therapeutic range – the mean increase was 16% in the Vitamin K group compared to 1.5% with placebo. A second, larger RCT done by Rombouts et al[24] assessing 100μg/day Vitamin K supplementation in 200 patients on phenprocoumon anticoagulation found that mean time in the therapeutic range was 85.5% in the placebo group and 89.5% in the vitamin K group [adjusted difference 3.6%; 95% CI -0.8% to 8.0%]. The time below the therapeutic range was 3.1% in the placebo group and 2.1% in the vitamin K group [adjusted difference -0.7%; 95% CI -2.5% to 1.1%] and the time above the therapeutic range was 11.4% in the placebo group and 8.5% in the vitamin K group [adjusted difference -2.9%; 95% CI -6.9% to 1.1%]. Despite being a larger study the results are not entirely applicable to practice patterns in North America for several reasons. First, the study used phenprocoumon instead of the more commonly used anticoagulant warfarin. While both are Vitamin K antagonists each drug has a different half-life in vivo. Prior studies have shown that longer half-life oral anticoagulants have a reduced risk of over-anticoagulation [INR>6][25] as well as providing more stable anticoagulation control[26, 27]. Second, while prior small studies looked at the effect of vitamin K supplementation in unstable patients on warfarin, this study enrolled all phenprocoumon anticoagulated patients regardless of stability of anticoagulation. The preceding fact is likely the cause of the lower treatment

effect size seen in this study relative to prior studies that exclusively evaluated intervention effectiveness in unstable patients. Such a result would have implications on the adoption of this intervention as a small treatment effect size when applying the intervention to a broad population [i.e. all patients being anticoagulated with Vitamin K antagonists] may not be sufficiently cost effective, thereby warranting targeted utilization of Vitamin K for those who have unstable control.

It should be noted that a literature search found an RCT [n=30] published after the initiation of this study by Dalloul et al[28] wherein unstable patients [defined at > 3 dose changes in the last 6 clinic visits due to out of range INRs] were randomized to oral vitamin K [175 μg daily] versus placebo for 6 months. The authors observed that there were no statistically significant difference in the mean number of dose adjustments after treatment [primary outcome measure] with vitamin K [3.9$\pm$2.8 vs. 4.0$\pm$2.1, p=NS]. A multivariate repeated measures model revealed that the number of warfarin dose adjustments were not significantly affected by treatment with vitamin K [F=1.06, p=0.313].

The rationale for conducting another study on the effectiveness of low dose Vitamin K at improving anticoagulation control is multifold. The most recent evidence based clinical practice guidelines on anticoagulation from the American College of Chest Physicians [ACP][29] makes a grade 2B recommendation [weak recommendation based on moderate quality evidence] that for patients receiving long term warfarin therapy and who have variable INRs not attributable to known causes of instability; a trial of low dose vitamin K [100-200μg/day] might be considered for stabilizing INRs. Given that prior studies involving warfarin anticoagulated patients were small, there exists a need for further studies to confirm the findings and contribute to the pool of available evidence if global practice is to change. Additionally, the most frequently cited RCT by Sconce and colleagues[23] used an

investigator formulated study drug (dispensed in liquid form). If the intervention of Vitamin K1 supplementation is to become broadly accepted then trials using commercially available Vitamin K1 preparations need to be evaluated. Another factor to consider is what if any impact known genetic polymorphisms that impact warfarin and Vitamin K metabolism could have on the success of this intervention. Several recent studies have shown that the presence of genetic polymorphisms that influence warfarin and Vitamin K metabolism can strongly influence a patient's maintenance dose and time spent within therapeutic range. For example, Cytochrome P450 2C9 *2 and *3 allelic variants are strongly associated with sensitivity to warfarin, resulting in a lower warfarin dose requirement, a greater risk of bleeding at initiation and maintenance, and a longer time to achieve a stable dose[30-32]. Variations in CYP2C9 have been found to account for 5-22% of inter-individual variability of warfarin dose requirements[33]. A matched case control study by Palereti et al[26] also found that Cytochrome P450 CYP2C9 variants *1/*3 or *2/*3 or *3/*3 were more frequent among cases with unstable coagulation control than stable controls [29% vs.15%; P=0.042]. Another important gene is the one that codes for VKORC1 [C1 subunit of Vitamin K Epoxide Reductase] -- in addition to being a crucial enzyme in Vitamin K metabolism, polymorphisms in the gene that codes for this enzyme account for over 37% of the pharmacological variability associated with warfarin dosing[34]. At the time of the initiation of this thesis, no study had looked at how genetic polymorphisms influence a patient's success at achieving stabilized INRs while on low dose Vitamin K supplementation.

1.4 Factors influencing Anticoagulation Control

A literature search was performed to identify published research on factors influencing anticoagulation stability. A formal systematic review was not a stated objective of this thesis nor its primary focus, hence specific commentary on the strengths and

weaknesses of the studies, plausibility of associations, and formal pooling of data were not performed. The results of this informal review were utilized to help the study investigators evaluate potential variables that may need to be accounted or standardized for in the randomized controlled trail. The decision as to which variables were to be collected was made from consultation with clinical hematologists and pharmacists on the basis of what had a strong association in the literature, was easily clinically measurable and relevant to care, and was measured by prior studies evaluating the effectiveness of Vitamin K on improving anticoagulation control. The search was updated as of January 22, 2011 and involved a search of EMBASE [1947 to 2011 January 21] and MEDLINE[R] In-Process & Other Non-Indexed Citations and MEDLINE[R] 1948 to 2011 January 21. The keywords used in the search were as follows: 1) exp International Normalized Ratio/ [8196 results] 2) Antocoagulation.mp [55185 results] 3) stability.mp [485319 results] 4) control.mp [3580575 results] 5) 1 or 2 [60375 results] 6) 3 or 4 [4014469 results] 7) 5 and 6 [6890 results]. Results from the search strategy were evaluated by reviewing the title and key words. A total of 131 papers were deemed to be potentially relevant for this review. Further examination of the abstracts, removal of duplicates, removal of foreign language entries that did not contain an English abstract, and the exclusion of one review article[35] due to inability to retrieve the paper through the university archives or grey literature resulted in 52 papers[36-49, 50-89] being included.

Age and anticoagulation instability have been reported in the literature as being associated with two of the studies reporting direct associations[14, 36] and one study reporting an inverse association[37]. O'Malley et al[36] in a retrospective review of a hospital drug information system found that older patients [> 70 years old] spent much more time outside of therapeutic range than those who were younger [30-59 years old]. Butchart et al[14] in a

prospective cohort study of patients who underwent single valve replacement noted that high anticoagulation variability was associated with age > 60 years at the time of the operation [p=0.002] and NYHA Class III or IV at 5 years post-op [p<0.001]. Rospond et al[37] in a case control study of eighty two patients found a trend that younger age was associated with increased risk of instability; however, it did not reach statistical significance [p = 0.13]. The probability of requiring a dosage change at monthly visits did correlate inversely with the duration of stable anticoagulation, from 16% to less than 8% at 2 months of stable anticoagulation, and tended to decline further with longer periods of stable therapy.

Duration of anticoagulation has been proposed as having an association with anticoagulation control. Copplestone and colleagues[38] in a retrospective chart review of two specialized anticoagulation clinics [430 patient years of data in 732 patients] observed that patients on long-term anticoagulation had better control than those on short term anticoagulation, as measured by percent time in therapeutic range -- 87% and 72% respectively.

Race has been purported by Bhandari et al[39] in a retrospective cohort study [N= 864 patients] as being associated with anticoagulation control. The mean time in therapeutic range for the authors' study population was 43% [included Caucasians, Asians, Pacific Islanders, Hispanics, and African Americans]. After adjustment, TTR was lower for African Americans than for Caucasians [absolute difference -8.7%, p< 0.001] and for Spanish-speaking than for English-speaking Hispanics [absolute difference, -7.2%, p< 0.05].

Patient personality traits and cognitive function were proposed in two respective studies as having an association to anticoagulation control. Harenberg et al[40] in a small retrospective review and questionnaire study of 28 patients suggested higher social competency [as measured by the Freiburger Persnlichkeitsinventar, FPI-R] and the less calm

and relaxed a person felt [as measured by SF12] was associated with a statistically significant decrease in the standard deviation of INRs in the preceding 6 months [p=0.0003 and p=0.013 respectively]. Flaker et al[41] in a subgroup analysis found an inverse relationship between cognitive function [assessed by the Folstein Mini-Mental Status Exam] and anticoagulation control. Other independent factors associated with a TTR <65% [below the median] in univariate analysis were region of the world, recent initiation of vitamin K antagonist, type of anticoagulant, and concurrent use of amiodarone or insulin. However, even after adjusting for these factors, lower MMSE scores still predicted a reduced TTR.

Adherence to anticoagulation therapy has been shown in several studies to be directly associated with anticoagulation control. Waterman et al[42] in a retrospective chart review of 347 patients [n=4305 INRs] attributed 36% of out of range INRs to warfarin or dietary non-adherence. Age younger that 65, age greater than 80, and living closer to the laboratory were predictive of nonadherence. Kimmel et al[43] evaluated the impact of adherence on anticoagulation control using Medication Event Monitoring System [MEMS] bottle caps in a prospective cohort of 136 patients. The authors noted that for each 10% increase in missed pill bottle openings, there was a 14% increase in the odds of underanticoagulation [p<0.001]. Participants with more than 20% missed bottle openings [1-2 missed days each week] had more than a 2-fold increase in the odds of underanticoagulation [adjusted odds ratio 2.10; 95% CI 1.48-2.96]. Participants who had extra pill bottle openings on more than 10% of days had a statistically significant increase in overanticoagulation [adjusted odds ratio 1.73; 95% CI 1.09-2.74]. Davis et al[44] in a cross sectional survey of 52 patients reported a statistically significant association between adherence (self reported 4 item Morisky survey] and good anticoagulation control [p=0.01]. Knowledge of warfarin therapy [assessed by self-administered questionnaire] and perceived impact on quality of life were not

significantly associated with anticoagulation control. Kumar et al[45] in a prospective cohort study of 30 outpatients found that compliance with therapy, using phenobarbitone as an indicator of compliance, was positively associated with anticoagulation control. It should be noted that unstable patients on entry into the study noticed a statistically significant improvement in INR control [p=0.0045] that was not replicated in those patients already having achieved stable control on study entry [p=0.36]. The authors of the study attributed the aforementioned fact to behaviour modification on the part of the unstable patients to increase compliance while in the study. Interventions aimed at improving adherence have shown some success at improving anticoagulation control in the literature. Nochowitz et al[46] in a cohort of 13 patients noted a significant decrease in the proportion of subtherapeutic INR values [60 +/- 25% to 35 +/- 29%; p = 0.04] and a significant improvement in the percent of time spent within the therapeutic INR range [32 +/- 22% to 56 +/- 28%; p = 0.03] with a warfarin adherence aid targeted at an inner-city clinic population.

An additional patient level factor that has been cited in the literature with a mixed degree of significance is the level of patient knowledge of anticoagulation and/or general numeracy/literacy. Both of the aforementioned factors would in theory influence whether the patient is performing appropriate behaviours during therapy that facilitate good control [i.e. ensuring consistent intake of Vitamin K foods, recognizing bleeding/bruising signs that could indicate supratherapeutic INR, attending scheduled INR tests, etc..]. A potential methodological issue in studies evaluating this association is the lack of consistent use of psychometrically validated questionnaires. Tang and colleagues[47] in a cohort study of 122 patients attending a specialized anticoagulation clinic in Hong Kong assessing knowledge of warfarin therapy [on the basis of 9 questions, max score 1.0] found that patients' overall knowledge was poor [mean score 0.48 $\pm$ SD 0.18]. Knowledge was related to age [r = -0.43,

p<0.001], duration of therapy [r = 0.18, p=0.044], and the number of INR values that were within target range in the most recent 4 clinic visits [r = 0.20; p=0.024]. Khan et al[48] in a before after study of 125 unstable patients on warfarin [measured by SD of INR > 0.5 in the preceding 6 months] randomized to usual care versus receiving education about warfarin; noted an increase in percentage of time in therapeutic range, bordering on significance, for the 6 months following education compared to the pre-education period [mean difference 8.8%, 95% C.I -0.2 to 17.8, p=0.054] . Khan and colleagues[48] also noted a statistically significant reduction in the standard deviation of INRs between the pre-intervention and pos-intervention period [Delta = 0.16; p=0.003]. The preceding differences were increased further when the intervention group received education and self-monitoring of their INRs [Mean difference 14.1, 95% C.I 6.7-21.5, p=0.10]. Estrada et al[49] in a prospective cohort study of 143 patients noted that patients with lower numeracy skills spent more time above therapeutic range [p=0.04] and had a trend of less time in therapeutic range [p=0.10]. However, time in range was similar among patients with different literacy levels [p=0.9]. However, as mentioned earlier not all studies have reported a positive association between knowledge/literacy and anticoagulation control. Fang et al[50] in a survey of 179 anticoagulated patients determined that limited health literacy [as measured by the short-form Test of Functional Health Literacy or s-TOFHLA] was not significantly associated with missing warfarin doses in 3 months [OR 0.9, 95% CI 0.4 to 2.0] nor with the proportion of person-time in therapeutic INR range [OR 1.0; 95% CI 0.7 to 1.4]. Esmerio et al[51] in a cross-sectional study of 140 patients at a specialized oral anticoagulation clinic utilized a structured questionnaire to obtain the clinical characteristics of the patients, their knowledge about the treatment, their compliance with the treatment [Morisky S test], and their

perception of the treatment. The authors noted a trend towards increasing TTR in patients with increased knowledge and compliance; however, it failed to reach statistical significance.

An additional patient level factor, and primary focus of this thesis, is the amount of dietary intake of Vitamin K – in particular the consistency of Vitamin K intake. Booth et al[52] was the first to publish a review stating that a diet with consistent Vitamin K intake could result in improved anticoagulation control. Pedersen et al[53] determined an association between Vitamin K consumption and anticoagulation stability in an RCT of 25 stable anticoagulated patients randomized to a high Vitamin K diet [median daily Vitamin K intake 1100 micrograms], low Vitamin K diet [135 micrograms], or habitual supplementation with 1000 micrograms of Vitamin K1 daily. Those who consumed a high Vitamin K diet were outside therapeutic range 69% of the time [95% CI 39-91%], no changes were observed in those on low Vitamin K diets, and all of the patients receiving Vitamin K1 supplementation were outside therapeutic range 100% of the time. Kurnik et al[54] in a case series of 3 patients suggested that for patients who were severely Vitamin K depleted [as measured by plasma Vitamin K levels < 0.1 ng/mL] increasing variability could be achieved with a multivitamin supplement delivering as low as 25μg Vitamin K1 daily due to proposed oversensitivity in these Vitamin depleted individuals to small amounts of Vitamin K supplements. Franco et al[55] in a prospective cohort of 39 patients demonstrated a statistically significant inverse association between Vitamin K intake and anticoagulation stability. Sconce et al[16] in a case control study that analyzed dietary records of 52 patients noting that the mean daily intake of Vitamin K in unstable patients was lower than that for stable patients in the two week study period [29$\pm$17μg vs 76$\pm$40μg]. Changes in vitamin K intake between weeks 1 and 2 of the study were negatively correlated with changes in INR amongst the unstable patients, however this failed to reach significance [r=-0.25; p=0.22].

Kim et al[56] evaluated the impact of Vitamin K intake on INR variability in patients on chronic warfarin anticoagulation [at least 1 year] using food diaries noting that as dietary vitamin K intake increases, stability of anticoagulation effect increases. Mean Vitamin K intake was 161.3 μg/day [Range 31.3-616.6 μg/day, N=61]. The coefficient of Variation [CV] for both INR and warfarin doses were negatively and independently associated with Vitamin K intake [r = -0.293, p=0.017 and r= –0.350, p=0.004, respectively]. The highest Vitamin K tercile [>195.7 μg/day] group had lower CV of INR than the low intake tercile [<126.5 μg/day group [19.2 ± 8.96 % vs. 25.5 ± 8.61 %, p<0.05]. Schrugers et al[57] in a systematic dose response study of supplemental Vitamin K1 in stable anticoagulated healthy volunteers found that the Vitamin K1 dose sufficient to override dietary variability, to cause a decrease in INR, was 150μg/day. Additionally they evaluated the effect of short term variability in Vitamin K1 intake [via a single spinach or broccoli meal] and found a short lived response that was unlikely to affect anticoagulation control as previously assumed. Furthermore, Schrugers and colleagues concluded that food supplements providing less than 100μg/day of Vitamin K1 should not significantly interfere with oral anticoagulant therapy.

A final patient level factor that has become more frequently evaluated in studies of patients on Vitamin K antagonists is the presence of genetic polymorphisms known to influence metabolism of Vitamin K [i.e. Vitamin K Epoxide Reductase VOKOR] and hepatic metabolism of Vitamin K antagonist [i.e. Cytochrome P450]. Lima et al[58] in a prospective cohort of 103 patients noted that patients with either CYP2C9*2 or CYP2C9*3 polymorphisms were difficult to maintain in the INR target range, showing significantly reduced ratio of adequate INR measures [0.54±0.2], when compared to CYP2C9*1*1 patients [0.63±0.2, one-sided p=0.038, Mann-Whitney U-test]. Patients with a CYP2C9*3 polymorphism, but not a CYP2C9*2 polymorphism, also required lower warfarin

maintenance doses [3.1±1.8 mg] than CYP2C9*1*1 patients [5.3±2.1 mg] with statistical significance [one-sided P=0.001, Mann-Whitney U-test]. Brasse et al[59] in a retrospective cohort of acenocoumorol anticoagulated patients noted that a combination of CYP2C9 [*2, *3] and VKORC1 [C1173T] polymorphisms had an increased risk of overanticoagulation compared individuals who were wildtype for one or both genes [hazard ratio, 3.8; 95% CI 1.6-9.1]. The time to achieve stability was prolonged in CYP2C9*3 allele carriers [mean difference 13.7 days; 95% CI 1.9-25.6]. Schalekamp et al[60] in a prospective cohort study of 284 patients noted that CYP2C9 polymorphisms were associated with a higher risk of overanticoagulation [INR>6.0] -- with CYP2C9*2 and CYP2C9*3 polymorphisms having hazard ratios of 3.09 [p<0.0001] and 2.40 [p<0.042] respectively. Additionally, carriers of CYP2C9*2 polymorphism were found to have a decrease likelihood of achieving stability with time to event analysis producing a hazard ratio of 0.61 [p=0.003]. Tassies et al[61] in a retrospective cohort of 325 acenocoumoral anticoagulated patients noted that carriers of CYP2C9*3 spent less time within the therapeutic range [64.7±23.1%] than did patients with the CYP2C9*1/*1 genotype [75.1±22.0%, p<0.01]; however, there was no statistically significant increase in bleeding frequency [19.0% vs.15.5%]. Palerti et al[26] in a case control study of 35 anticoagulation clinics in Italy who referred unstable patients [no apriori criteria were established for unstable] found that cases [n=77] were more likely than controls [n=80] to have INRs greater than 4.5 [12.4% vs 0.4%, p<0.001]. Factors associated with increasing instability in the Palerti et al[26] study were: working people [versus pensioners], acenocumourol usage [versus warfarin], and low compliance/low knowledge of oral anticoagulation therapy. As stated earlier in this thesis manuscript, Palerti and colleagues also noted an increased prevalence of CYP2C9 variants among unstable cases relative to stable controls [p=0.042].

While the aforementioned studies point to numerous patient level factors, the presence of treatment related factors have also been shown to have an impact on anticoagulation control. One of the most frequently reported in the literature is the concomitant use of medications known to interact with warfarin – mainly those that either potentiate or inhibit warfarin metabolism via influencing Cytochrome P450 hepatic metabolism. Verhovsek et al[62] in a retrospective chart review of anticoagulated patients [N=78.2 patient years of data] at long term care facilities noted that 79% of residents were prescribed at least one interacting medication in the review period [12 months]. Residents receiving interacting medications spent less time in the therapeutic range relative to those not receiving interacting medications [53.0% vs. 58.2%, OR = 0.93, 95% CI 0.88 to 0.97, p = 0.002]. Smith et al[63] in a retrospective cohort study noted that the percentage of INR results within target range was inversely associated with the number of new drugs started within the year [Spearman's $\rho = -0.15$, p=0.042]. The percentage of INR results in target range was not associated with the number of drugs stopped in the year [p=0.82], the number of drugs used intermittently [p=0.74], or the number of medications taken continuously [p=0.10]. However, the percentage of INR results below target range was associated with the number of medications taken continuously [$\rho = -0.17$, p=0.041] and the number of new drugs started [$\rho = 0.29$, $p<0.001$]. Due to the fact that many reports of warfarin-drug interactions in the literature are of varying methodological quality; the investigators of this study utilized a systematic review by Holbrooke et al[64]. In this review, the authors conducted a thorough evaluation of medication and food interactions with study quality and severity of interaction assessed by clinicians to produce of list of interactions by likelihood. Medications deemed by the authors of this review to be "highly probable" or "probable" of causing an interaction effect were evaluated in this study.

An additional treatment related factor that has been shown in the literature to be associated with anticoagulation control is the type of anticoagulant used – in particular, longer half-life Vitamin K antagonists are associated with improved control relative to those with shorter-half-life. Amian et al[65] in a prospective cohort study evaluating the stability of warfarin versus acenocuomoral found warfarin to be associated with more stable anticoagulation control with a statistically significant lower incidence of all hemorrhages [p=0.008]. Fihn and colleagues[27] also noted in a retrospective cohort study that patients on phenprocoumon were within the therapeutic range 50% of the time compared with 43% for acenocoumarol [OR 1.32, 95% CI 1.24-1.41]. Moreover, patients on phenprocoumon required 15% fewer monitoring visits since the INR values were more stable.

One of the most significant treatment related factors associated with anticoagulation control is the management setting. Positive management variables shown in the literature include: specialized anticoagulation clinics, patient-monitoring/management of INRs, and computer assisted dosing.

Numerous studies have pointed to the fact that specialized anticoagulation clinics [in particular pharmacist run anticoagulation clinics] achieve superior control relative community based management by physicians. Cohen et al[66] in retrospective review of dedicated pharmacist managed anticoagulation clinic versus VA medical centre clinic did not show a statistically significant difference in stability as measured by prothrombin time in range. However, dedicated pharmacist clinics did have fewer complications per treatment year [6.9% vs. 9.0%]. Garabedian-Ruffalo et al[67] in a before after study of patients referred from the community to a dedicated pharmacist managed anticoagulation service had decreased percentage of patients requiring hospitalization 39% vs 4% and decreased percentage of prothrombin times outside of therapeutic range 35.8% versus 14.4% when

compared to the pre-intervention period. Wilt et al[68] in a retrospective chart review of 28 patient years of data from a family practice group with patients having anticoagulation monitoring via pharmacist [experimental group] versus physician [control group] found a greater incidence of complication [thromboembolic events and bleeds] in the physician monitoring group RR=20 [95% CI 5-87]. Chiquette and colleagues [69] in a prospective cohort study of a pharmacist–run anticoagulation clinic [AC] showed improved outcomes relative to usual physician care. Improved outcomes included improved anticoagulation control as measured by fewer INRs > 5.0 [7.0% vs 14.7%], improved time in therapeutic range [40.0% vs 37.0%], and decreased time spent with INR > 5 [3.5% vs 9.8%]. Additionally reduced major bleeding [1.6% vs 3.9%] and thromboembolic events [3.3% vs 11.8%] were found to be statistically significant. The authors estimated that the pharmacist run AC clinic could have saved $162058 per 100 patients annually in reduced hospitalizations and emergency department visits. Van Walraven et al[70] in a systematic review and meta-regression of 67 studies [N=57,154.7 patient years of data] found that study setting had the most profound impact on anticoagulation control with community practices having significantly lower control than specialized clinics or clinical trials [-12.2%; 95% CI -19.5% to -4.8%; p<0.0001]. Patient self management of anticoagulation was also associated with improved time in therapeutic range [7.0%; 95% CI 0.7% to 13.3%; p=0.03]. Dolan et al[71] in a systematic review of 36 studies of anticoagulated atrial fibrillation patients found that percent time in therapeutic range was significantly higher in specialist care settings relative to usual care [+11.3% 95% CI 0.1-21.7%]. Naive anticoagulant users also spent less time in therapeutic range than existing users [56.5% vs 61.2%]. Chamberlain et al[72] also observed in a retrospective record linkage study that specialized anticoagulation clinic patients had fewer INR values outside the target range [+/- 0.1] than the traditional primary

care group [40.4% vs 47.3% p = 0.022]. The anticoagulation clinic group also had significantly fewer INR tests drawn more than 6 weeks apart than the traditional care group [3.7% vs 8.1% p = 0.01]. Witt et al[73] in a retrospective cohort study of 6645 patients on warfarin therapy noted that patients in a pharmacy anticoagulation service had higher TTR relative to control physician management [63.5% vs 55.2%, p<0.001]. Baker et al[74] in a meta-analysis observed that community usual care setting spent less time in range compared with specialized anticoagulation clinic spent 11% [95% CI 2%-20%, n = 6 studies with 9 study groups].

While the aforementioned literature demonstrates that specialized anticoagulation clinics have superior control relative to community physician management a few studies did fail to show superiority. Radley et al[75] in a before-after study evaluating assessing 2219 INR results for 383 patients during a handover from pharmacist led anticoagulation to junior medical staff saw no statistically significant difference in anticoagulation control for stable patients [defined as having INR in range prior to the handover and being in range after the handover], as measured by proportion of INRs out of range. Pell et al[76] in an observational study evaluating the impact of treatment setting on anticoagulation control did not demonstrate superiority of dedicated hospital anticoagulant clinics relative to general practice management; however, they did observe that general practice patients required more frequent visits for review of anticoagulation with median interval between visits of 16 days and 42 days in general practice and hospital anticoagulation clinics respectively, p<0.001.

Self-monitoring [wherein patients check their INRs with Point of Care devices] and Self-management [wherein patients monitor their INRs and make adjustment to anticoagulant doses] have both been shown in the literature to improve anticoagulation outcomes. Ansell et al[77] in the first long term study to evaluate patient self-monitoring and

self-management of warfarin [matched case control study of 40 patients] showed that patients were capable of achieving anticoagulation control better than specialized anticoagulation clinics [% Time in therapeutic range 88.6% vs 68.0%, p<0.001]. Dauphin and colleagues[78], on the other hand, in a preliminary analysis of 67 patients in an open label RCT of monthly lab monitoring versus weekly self-monitoring found no statistically significant change in time spent in target range [p=0.45]. However, for patients outside of the target range, the absolute mean deviation of the INR from the target range was found to be significantly less in the self monitoring group relative to the control group [p=0.0004]

An additional treatment level factor impacting anticoagulation control is the use of computer assisted dosing and even the adoption of simple aids [i.e. dedicated anticoagulant charts]. Galloway et al[79] showed that adoption of computer assisted warfarin dosing programs could decrease staff workload and increase the proportion of patients who achieve their target therapeutic range. In the study, the proportion of patient's who achieved a target range of 2.0-3.0 rose from 55% to 72%. Fitzmaurice and colleagues[80] in an RCT of 49 patients randomized to be dosed by computer decision support versus primary care clinical dosing found improved anticoagulation control associated with the use of the computerized decision support [p<0.001; McNemar's test of dependent proportions]. Gouin-Thibault et al[81] in a prospective observational study determined via multivariate analysis that model of care [computer generated dosing vs. standard physician based care] was significantly associated with greater percent time in therapeutic range in the intervention group relative to the standard care group [59% vs 48%, P=0.004]. Phillips et al[82] in a before-after study noticed that the introduction of dedicated anticoagulation charts for patients on Coumadin decreased the percentage of time spent over-anticoagulated [INR>4.5] from 5.4% to 2.7% [p<0.001].

Hospitalization and the peri-hospitalization period have also been showed in two large studies to influence the degree of anticoagulation control. Van Walraven and colleagues[83] determined from a retrospective cohort study using administrative databases [N= 7179 patients; 3238 patient years] in Eastern Ontario that hospitalization is inversely associated with anticoagulation control. The mean proportion of days in therapeutic range [PDTR] was 59.2%; hospitalization independent of all other factors was associated with a 15% decrease in the PDTR [RR 0.85, 95% CI 0.83-0.87)]. Hospitalization was also independently associated with greater proportion of time with a critically low INR [RR 1.68, 95% CI 1.51 - 1.88] and a critically high INR [RR 1.70, 95% CI 1.38-2.08]. In a separate study using ARIMA modelling of administrative data, Van Walraven et al[84] also noted decreased anticoagulation control in the perihospitalization period. Before hemorrhagic admissions, mean INR and proportion with INR>5 increased significantly [daily increase 0.024, p=0.03 and 0.2%, p=0.01]. Following other hospitalization types, the proportion of patients with INR<1.5 was significantly increased [daily increase 0.19%, p=0.02].

Numerous cohort and case control studies have also attempted to use multivariate regression analysis to quantify the relationship and strength of many of the aforementioned patient level and treatment level variables to anticoagulation control. Vogel et al[85] in a prospective study of 110 geriatric patients found that of 11 predefined variables, only cancer [history of or current] was associated with elevated INR. Smith et al[63] in a retrospective cohort study noted that the percentage of INR tests in target range was significantly associated with patients having a heart valve replacement [IQR % TTR 48.7% with heart valve vs 67.4% without a heart valve, Mann-Whitney U test, p=0.006]. No association was found for patients with atrial fibrillation, heart failure, prior cerebrovascular accident, prior thrombosis, or ongoing diabetes mellitus. Witt et al[86, 87] in a retrospective cohort study

[n=6073 patients] assessed via multivariate logistic regression factors associated with stable control [defined as having INR values exclusively in range] compared to unstable control [having at least one INR out of range]. Predictors of stable control included age > 70 years, absence of comorbid heart failure, male gender. A subsequent analysis of outcomes at 12 months[87] noted that bleeding and thromboembolic complications were significantly lower in stable vs. unstable comparator patients [2.1% vs. 4.1% and 0.2% vs. 1.3%, respectively; $p < 0.05$]. Cavallari et al[88] in a case control study of 60 African American patients collected data on INR, warfarin dosing, adherence [self declared], vitamin K intake, acute illness, alcohol intake, bleeding and thrombotic complications, VKORC1 polymorphisms, CYP2C9 polymorphisms, and changes in concomitant medications. The authors found on univariate analysis that higher warfarin doses, lower adherence, vomiting/diarrhoea, and use of anti-infective agents were more common among unstable patients. VKORC1 and CYP2C9 polymorphisms were not associated with anticoagulation stability on univariate analysis. After multivariate regression analysis, only poor adherence and gastrointestinal illness remained predictive of unstable anticoagulation. In a control group of Caucasians of similar age and sex distribution, poor adherence, but not gastrointestinal illness, was associated with unstable anticoagulation. Costa and colleagues[89] in a prospective cohort concluded via multivariate linear regression [N=134 patients] that good quality anticoagulation [TTR $\geq$ 66%] was independently associated with male gender [OR 2.41; 95% CI 1.06-5.49], presence of family support [OR 3.32; 95% CI 1.16-9.48], no alcohol regular use [OR 8.59; 95% CI 1.45-51.09], good medication management capacity, as assed by Drug Regimen Unassisted Grading Scale [OR 4.18; 95% CI 1.63-10.68], more than 2 months since anticoagulation start [OR 3.23; 95% CI 1.25-8.36] and regular vitamin K intake, expressed by its variability in μg/kg/day [OR 0.79; 95% CI, 0.64-0.98]. Rose et al[90] in a retrospective

administrative database analysis of 124,619 patients who received oral anticoagulation from the Veterans Health Administration noted several patient level predictors of percent time in therapeutic range [TTR] via multivariate regression during the maintenance phase. Predictors of decreased TTR included hospitalizations [four or more hospitalizations in the two year observation period of the study -9.4%], increased medications [16 or more medications in the two year study period -5.1%], alcohol abuse [-5.4%], female sex [-2.9%], cancer [-2.7%], dementia [-2.6%], non-alcohol substance abuse [-2.4%], and chronic liver disease [-2.3%].

Based on the above review, the authors of this study utilized the findings along with consultation with clinicians to determine relevant variables that should be collected in this study. With respect to clinical variables, we chose to collect information on age[14, 36, 37, 86, 87], gender[86, 87,89, 90], alcohol use [86, 87,89, 90], and race[39] which have shown evidence in the literature of being associated with anticoagulation control. Based on a prior study performed by the authors[102], it was determined that there may be utility in collecting data from patients on BMI, BSA, Height, Weight, Exercise, and specific comorbidities (cancer, diabetes, hypertension, renal failure, and inflammatory bowel disease). The rationale being that the aforementioned variables were found to be associated with warfarin maintenance dose on univariate and/or multivariate analysis in our patient population. Higher maintenance doses have been associated with increased risk of unstable anticoagulation control[88], hence the collection of these variables may provide an explanation for potential confounders in anticoagulation control. Adherence[42-45] to anticoagulation has also been shown to be associated with anticoagulation stability. With respect to potential confounders to adherence that may impact evaluation of anticoagulation control, analysis of the literature demonstrated an association between adherence and age[42] and a non-significant association with

knowledge[44] of warfarin therapy. Anticoagulant related knowledge and health literacy was deemed to be a variable that should be evaluated given its varying associations with anticoagulation control, with both positive[48-50] and non-significant associations[51] being reported in the literature. Knowledge has been shown in the literature to be inversely associated with age[47]. With respect to Vitamin K intake, it was felt that it would be a potentially useful variable to collect in order to verify prior research[57] that the dosage of Vitamin K utilized in this study (200 micrograms/day) is indeed sufficient to override dietary variability in Vitamin K intake. Polymorphisms in genes known to impact Vitamin K and warfarin metabolism (i.e. CYP2C9*2 polymorphisms, CYP2C9*3 polymorphisms, VKORC1 -1636 G>A polymorphism, CYP4F2 1173C>T polymorphisms) were deemed to be relevant for this study. Prior studies have shown associations between these polymorphisms and anticoagulation stability[26,58-61]. The concomitant medications that a patient would be on during this study were deemed to be a relevant variable to capture as the aforementioned literature has shown an association between anticoagulation stability and number of concomitant medications[90] as well as concomitant use of interacting medications[62]. Any new drugs initiated during the study period would also be captured due to a prior study that illustrated an inverse association between anticoagulation stability and the number of new drugs started[63]. The choice of instruments to evaluate adherence, medication usage, knowledge, and Vitamin K consumption are summarized below within the methods section.

2. AIMS AND OBJECTIVES

2.1 Primary Objective:

To evaluate the effectiveness of low dose Vitamin K [200 μg per day] relative to placebo at improving anticoagulation control in patients with unstable anticoagulation control [defined as ≥ 3 INRs out of range or ≥ 3 dose changes in the preceding 6 months].

2.2 Secondary Objectives:

To evaluate the impact on anticoagulation control in the intervention and control arms of clinical demographic variables, concomitant interacting medications, patient knowledge of anticoagulation, and genetic polymorphisms in genes for CYP450 2C9, VKORC1, and CYP450 4F2.

2.3 Outcome Measures of Anticoagulation Control:

Primary outcome measure:

1. Change score in percent time in therapeutic range [% TTR] between 6 month pre-intervention and 6 month intervention period for Vitamin K and placebo groups

Secondary Outcomes measures:

1. Change score in Standard deviation of INRs between 6 month pre-intervention and 6 month intervention period for Vitamin K and placebo groups
2. Change score in Number of out of range INRs between 6 month pre-intervention and 6 month intervention period for Vitamin K and placebo groups
3. Change score in Number of dose changes between 6 month pre-intervention and 6 month intervention period for Vitamin K and placebo groups

3. METHODS

3.1 Study Design

The design of the study was a prospective, placebo controlled, double-blinded, randomized controlled trial with recruitment from the hospital-based Thrombosis Clinic at the Ottawa Hospital, Civic Campus. Patients were randomized to either the intervention arm receiving two tablets once-daily containing 200µg of Vitamin K [Swanson Health Products, USA, Lot Number SW994] or the placebo arm consisting of two tablets once-daily containing placebo [Odan^{TM} lactose based placebo].

Patients did not have their anticoagulation management altered in any other way; rather they continued to be followed up for a period of six months at the Thrombosis Clinic to examine measures of anticoagulation control. Improved control was assessed by calculating change scores in Percent Time in Therapeutic Range [calculated by Rosendaal Method] between the six month study period and the immediate six months prior to enrollment. Multivariate linear regression modelling was also be utilized with the mean intervention outcome measure score (% TTR, Standard deviation of INRs, Number of Dose Changes, Number of INRs out of range) as the independent covariate. Sample size calculation will power the study to detect an absolute difference of 10% in the mean change score of percent time in therapeutic range between the intervention and control groups [difference of means].

3.2 Eligibility criteria

Inclusion Criteria

1) Adult [$\geq$ 18 years of age]
2) Have been on warfarin anticoagulation for at least 7 months

3) Have an INR target range of 2.0-3.0.
4) Are defined as having "unstable" control of anticoagulation [as defined by Ford et al[20]]: In the preceding 6 months, the patient has had at least 3 warfarin dose changes or at least 3 INRs outside target range
5) Able to provide written, informed consent

Exclusion Criteria

1) Anticipated interruption or termination of warfarin anticoagulation in the next 6 months [26 weeks] for a period of 1 week or greater
2) Patient instability in preceding 6 months suspected to be due to interruption of warfarin therapy during the past six months for 1 week or more **or** due to significant non-compliance with warfarin
3) Possess a known allergy to Vitamin K or lactose-based placebos.
4) Currently taking supplements or multivitamins that contain Vitamin K [in doses of 25µg/day or greater]

3.3 Rationale for Inclusion/Exclusion Criteria

The rationale for choosing patients who have undergone at least 7 months of warfarin anticoagulation is to ensure that, excluding a 1 month induction period when a patient is beginning warfarin and likely to be undergoing dose changes with fluctuating INRs, there is at least six months of data for each patient during which they should be stable. We chose to look at an INR range of 2.0-3.0 because this is the preferred target range of anticoagulation for most clinical indications in North America. Previous studies using the European target ranges of 2.5-3.5 may not be comparable to North America since there is anecdotal evidence

from our clinical database that higher target ranges are associated with greater risk of instability [as measured by decreased Percent Time in Therapeutic Range].

In choosing our definition of instability [Inclusion Criteria 4], we kept in mind that the definition had to be one that any clinician could identify in their patients. Definitions that implement an assessment of INR standard deviation [i.e. Sconce et al[23] defined instability as having an INR standard deviation in the preceding 6 months of > 0.5 and at least 3 warfarin dose changes] or which require complex calculations [i.e. Palereti definition[26] which requires at least 40% of visits in the preceding 4 months to have a dose change that is greater than 15% of the preceding dose] are not likely to be recognized or utilized by anticoagulation providers that don't have access to specialized software to confirm eligibility. Therefore, the authors of this study took a pragmatic approach and chose a definition that could be easily assessed by any anticoagulation provider – from family physician to pharmacist in specialized anticoagulation clinic. Furthermore, by choosing a broad definition it allows for subgroup analyses should a more stringent definition be required.

In our exclusion criteria, we excluded patients for whom instability was due to interruption of warfarin for a period of $\geq$ 1 week [Exclusion Criteria #2; assessed by presence of documented interruption in the patient's electronic anticoagulation record in 6 months preceding enrolment]. Exclusion criteria #2 also excluded patients with ***significant*** non-compliance on warfarin therapy. Non-compliance on warfarin therapy was defined as either non-compliance with taking warfarin or non-compliance with attending INR monitoring. Non-compliance with INR monitoring was defined by presence of at least one documented conversation, in 6 months preceding enrolment, in the patient's DAWN^{TM} anticoagulation record by a clinic member for missed INR appointments. The practice at our clinic is that once a patient has missed three INR monitoring appointments they are called by

the clinician or INR clerk to discuss the importance of attending regular monitoring. Non-compliance with taking warfarin was defined as the patient having documented self-reported missed doses at least one-third of their INR/dosing entries in DAWN^{TM} in 6 months preceding enrolment. Previous efficacy studies such as that by Sconce et al[23] study also excluded patients who: were using [or changed their usage] of medications known to interact with warfarin, had comorbidities known to interact with warfarin, had irregular or excessive consumption of alcohol, or suspected non-compliance. We believe that while these conditions may be appropriate in an efficacy study – they are not completely appropriate when assessing effectiveness in real world clinical practice.

3.4 Recruitment Methodology

The recruitment strategy utilized in this study involved several approaches. Firstly, patients meeting the inclusion criteria were referred to the investigators by clinic physicians or the clinic pharmacist [responsible for dosing and managing patients] where they were provided with a recruitment letter and access to a clinical research coordinator (Habeeb Majeed) to answer any questions. An additional approach to recruitment involved searching active patients in the DAWN database who met our inclusion criteria. The DAWN database is a clinical database using commercially developed software for managing patients on long-term warfarin. The database is maintained by the Thrombosis Clinic and includes data on all patients taking long-term warfarin [~1400 active patients at time of study initiation]. The principal investigator of this study [Dr. Phil Wells], as well as 2 study co-investigators [Dr. Marc Rodger and Habeeb Majeed], had authorized access to this password-protected database which was stored on the Ottawa Hospital's shared server [J:/apps/Dawn/pract]. Patients meeting the required definition of stability were sent a recruitment letter soliciting

their participation in the trial. The recruitment letter was followed up with a phone call approximately 2 weeks from the mailout to evaluate patient interest in the study.

3.5 Sample Size Justification

A sample size of 46 patients per arm was calculated to provide 80% power to detect an absolute difference of 10% in the change score [% TTR in 6 month study period - % TTR in 6 month pre-intervention group] between the intervention and control arms, using a two-sided t-test at the 5% level of significance, assuming a standard deviation of σ =17%, [Sconce et al[23]]. The rationale for choosing a minimally clinically important difference [MCID] of 10% was several-fold. First, consultation with stakeholders at the Ottawa Hospital Thrombosis clinic [pharmacist, haematologists, and nurses] suggested that an absolute improvement of 10% in TTR would be significant to warrant adopting this intervention. Additionally, as determined from our prior literature review Samsa and Matchar[10] suggested basing sample size calculations on a 5-10% absolute improvement in TTR in their literature review evaluating patient self-management of anti-coagulation. Finally, Van Walraven et al[11] also determined in a Monte Carlo simulation study that a change in % TTR of 8.4% [Range 1.8-18%] was associated with a decrease in hemorrhagic and thrombotic event; however, it did fail to meet statistical significance. Therefore, based on the above factors, the authors of this study chose an MCID of 10% absolute improvement in the change score of TTR.

3.6 Randomization and Allocation Procedure

Patients who consented to participate in the study were randomly assigned to the 200μg/day Vitamin K supplementation group or Lactose based placebo group. A computer generated randomization list was generated using randomly permuted blocks of fixed size 4.

The randomization list, prepared by a biostatistician independent of the investigators/statisticians analyzing this study, was provided to an independent pharmacy that compounded the Vitamin K or Placebo for each patient. Each opaque prescription bottle contained a six-month supply of the investigational drug product along with the patient ID number for whom it was intended. The rationale for using a fixed block size in our randomization list was to allow the investigators to have balanced groups for each batch of investigational drug produced. Each batch consisted of sufficient investigational drug for 16 patients – 8 allocated to the placebo arm, 8 allocated to the intervention arm; thereby minimizing excess product being present should recruitment be less than expected.

Measures to ensure adequate allocation concealment included having compounding of the investigational product being performed by separate pharmacists to those managing patient anticoagulation. Furthermore by using sealed opaque bottles to dispense the 6 month investigational drug limits the opportunity for the investigator or patient to know the identity of the medication.

3.7 Baseline Visit and Data Collection

At the baseline study visit, demographic and clinical variables were collected including: age, sex, height, weight, race, bleeding history, comorbidities, and usage of medications known to interact with warfarin. Additionally, INR and dosing history for the most recent six months prior to entering the trial were obtained from the DAWN database. The aforementioned information was used to determine within the 6 months preceding enrolment: the standard deviation of INRs, the percentage of time within therapeutic range, the number of dose changes, the number of INR measurements out of range, the mean duration between INR measurements, and the mean duration between dose changes. All enrolled patients were then asked to complete four questionnaires at their baseline visit.

The first questionnaire, completed by the subject, was the Brief Medication Questionnaire [BMQ] used to assess medication adherence and self-efficacy. The rationale for choosing the BMQ came from its use in the Sconce et al[23] study where it was used to eliminate patients who had the potential for non-adherence. Additionally, a review of validated instruments [MAQ, BMQ, SEAMS, Hill-bone Compliance Scale] to assess medication adherence by Lavsa et al[91] confirmed that while there is no gold standard adherence scale, the BMQ is effective in assessing adherence and self-efficacy. As stated in the review by Lavsa et al[91] the BMQ was constructed by Svarstad et al[92] with the goal of creating an instrument that is brief, sensitive, and able to detect different types of nonadherence. The scale consists of a five-item regimen screen to detect repeat and sporadic nonadherence, a two-item belief screen to assess beliefs about drug efficacy and bothersome effects, and a two-item recall screen to identify difficulties in remembering medication-taking behaviour. The BMQ was initially validated in patients prescribed the angiotensin converting enzyme inhibitors enalapril or captopril. The regimen screen had a sensitivity of 0.8 and a specificity of 1.0 for detecting repeat nonadherence, which was defined as over- or undertaking the prescribed number of doses by 20% or more. The belief screen has a sensitivity of 1.0 and a specificity of 0.8 for identifying repeat nonadherence. The recall screen has a sensitivity of 0.4 and a specificity of 0.4 for detecting repeat nonadherence. BMQ also has been used extensively in the literature for numerous chronic diseases[93-95].

The second questionnaire, completed by the subject, was the Anticoagulation Knowledge Assessment [AKA], a validated instrument to evaluate patient knowledge of anticoagulation therapy. A review by Wofford et al[96] determined that out of 17 instruments reported in the literature only two were formally validated. The Oral Anticoagulation Knowledge Test [OAK][97], a 20 item questionnaire, where investigators evaluated construct

and content validity, test-retest reliability, and internal consistency reliability. The Anticoagulation Knowledge Assessment [AKA][98], a 29-item instrument written at the 7th grade level covering 9 content areas, including medication, medication administration, medication interactions, activity, diet, side effects, informing health care providers, procedures, and lab monitoring. Content validity was assessed using Marzano's Taxonomy and reliability using Rasch dichotomous model. The AKA questionnaire was employed in our study because of its range of topics relevant to the patient taking warfarin. The research assistant provided the questionnaire (either in French or English) for the subject to complete at the baseline visit. Research coordinators were instructed not to assist subjects in completing the questionnaire. Subjects were instructed that should they not know the answer to a question to leave the question blank instead of guessing a response.

The third questionnaire, completed by the researcher, was a list of all of the patient's concomitant medications, including vitamins/minerals and supplemental natural health products. A note was made by the clinical research coordinator if the patient was taking any medications known to interact with warfarin [defined as showing a "highly probably" or "probable" association in the review by Holbrooke et al[64]].

The final questionnaire, to be completed by the subject at home, was a baseline assessment of Vitamin K consumption [modified K-card]. Given that many foods do not contain significant Vitamin K levels, food diaries were determined to be more labour intensive and would not yield as much useful data as the K-card. The K-card was a validated self-assessment instrument developed by Couris et al[99] to determine daily variations in dietary vitamin K1 [phylloquinone] intake for use in patients receiving oral warfarin anticoagulant therapy. The K-card was validated in a population [n=36] who had completed dietary records and prior plasma concentrations of Vitamin K1. The mean dietary

phylloquinone intake [+/- SEM] was 138.8 +/- 15.7 μg for the K-Cards compared to 136.0 +/- 15.8 μg for the diet records [p = 0.067]. Bland-Altman limits of agreement between quantities of dietary phylloquinone calculated from the K-Card and values obtained from the weighed food records were +/- 38μg. In producing a modified K-card, the authors of this study incorporated all foods listed in the original K-card as well as foods listed in the *USDA National Nutrient Database for Standard Reference, Release 18 Vitamin K Content of Foods* as having a Vitamin K1 content of 25 μg /serving. The rationale for modifying the original K-card was due to the fact that the initial instrument was derived in a prodominantly American (Caucasian) population who did not consume many foods often associated with high Vitamin K content (i.e. Bok Choy). Given the multicultural nature of the Canadian populace it was determined by the investigators that foods that had the potential to increase Vitamin K1 content by 25 μg /serving should be included. The rationale for choosing 25 μg as a threshold came from a case series by Kurnik et al[54] which demonstrated that for patients who were severely Vitamin K depleted [as measured by plasma Vitamin K levels < 0.1 ng/mL] increasing variability could be achieved with a multivitamin supplement delivering as low as 25μg Vitamin K1 daily. The rationale for using the K-card was to confirm that the Vitamin K1 dosage utilized in the trial [200 μg/day] was sufficient to over-ride patient dietary variability in Vitamin K intake. The aforementioned fact is highly likely, given the prior dose response study by Schurgers et al[57] from which Sconce et al[23] determined that a Vitamin K1 dose of 150μg/day was sufficient to over-ride dietary variability.

Upon completion of the baseline data collection, a research staff member trained in phlebotomy extracted 3 sodium citrate tubes of blood from the patient at the level of the antecubital fossa. The purpose of the blood sample was for baseline INR measurement as

well as plasma banking and genotyping [for the presence of genetic polymorphisms: CYP2C9*2, CYP2C9*3, VKORC1 -1639 G>A, and CYP4F2 C>T].

3.8 Genotyping

Using blood collected from the sodium citrate vacuum tubes designated for genotyping, DNA was extracted from peripheral blood leukocytes [buffy coat] using standardized kits.

Forward and reverse primers for 4 polymorphisms (CYP2C9*2, CYP2C9*3, VKORC1 -1639 G>A, and CYP4F2 1347 C>T) were designed and tested to amplify regions surrounding each SNP. Multiplex PCR was carried out in a reaction volume of 30 µl containing 100 ng DNA, 2X reaction buffer (2.5 mM MgCl2), 1X Qiagen Q-solution, 0.4 mM each dNTP, 0.4 µM each primer, and 2.5U Qiagen taq. The cycling conditions utilized in this study were as follows: an initial denaturation at 94 °C for 4 minutes then 30 cycles of 94°C for 1 minute, 60°C for 1 minute, and 72°C for 1 minute followed by a final extension at 72°C for 5 minutes. PCR products were verified on a 2% agarose gel.

SNP genotyping was performed using the ABI Prism SNaPshot Multiplex Kit (Applied Biosystems, Foster City, CA, USA). In this reaction an unlabelled primer, designed to be complementary to the region immediately adjacent to each SNP, is extended by a single fluorescently labelled ddNTP at the SNP site. Primers for each of the four SNPs were designed to be of different lengths in order to distinguish them when the mixture is electrophoresed. The single base extension took place under the following cycling conditions: 96 °C for 10 seconds, 50 °C for 5 seconds and 60 °C for 30 seconds for 25 cycles. The mixture was treated with 1U SAP (USB) to remove unused ddNTPs, and then held at 95 °C for 5 minutes to denature the extended primer from the PCR product.

Samples (2 µl each) were loaded onto the Applied Biosystems 3130xl Genetic Analyzer with 8 µl of formamide (Applied Biosystems) and 0.2 µl of GeneScan -120LIZ Size Standard (Applied Biosystems) and electrophoresed. Analysis was performed using GeneMapper Software Version 4.0 (Applied Biosystems).

3.9 Follow-up Data Collection

Upon initiation of the study medication, patients were required to have their INR monitored weekly and, if necessary, their warfarin dose was adjusted to counteract any subtherapeutic or supratherutic INRs. As soon as two consecutive INR measures were found to be within target range; the patient resumed INR testing at a frequency set by their clinician [i.e. clinic pharmacist] for managing their anticoagulation therapy.

Patients enrolled in the trial received follow-up phone calls/emails once a month during the six month study period during which time they were asked : whether there had been any changes to their health status since the last follow-up, have they been experiencing any complications or allergic reactions to the study medication, have they had any changes in the prescription medications they are taking especially medications known to interact with warfarin, and whether they have missed any warfarin/study medication doses. Patients were instructed to complete the K-card at the 2 month, 4 month, and 6 month time intervals whereafter they were to return them to the investigators in a provided postage-paid envelope or via email. Follow-up phone calls/emails were used to contact non-respondents.

3.10 Handling of Missing Data and Treatment Crossover

The most critical data in this study were the INR and dosing values pre- and post-intervention. The importance of attending regular INR monitoring continued to be emphasized to patients to ensure safety during anticoagulation. A scenario where the patient

would have insufficient INRs to complete measures of anticoagulation control over the six month study period was unlikely since clinical protocols are utilized to ensure follow-up promptly if a patient misses a scheduled INR test. However, should a patient have insufficient INR/dose values to determine whether the intervention is effective, the protocol would involve exclusion of that patient from analysis and reporting of this fact in the results section. Failure to complete a follow-up K-card questionnaire did not exclude a patient from analysis provided there was sufficient INR/dose information.

Since supplemental Vitamin K tablets were not readily available for purchase in Canada during the time of the study, the likelihood of contamination or treatment group crossover was highly unlikely. However, patients were also asked to self-report any change in medications and supplements taken during the study period to their clinical pharmacist and to the study coordinator at follow-ups to evaluate for potential confounding.

3.11 Statistical Analysis

The effectiveness of randomization was evaluated by comparing descriptive statistics of the baseline demographic and clinical variables between the placebo and intervention groups [Table 1]. The comparison of ordinal variables between the intervention and control groups were evaluated using Chi-square (for rxc) analysis with the chi-square statistic being utilized when its underlying assumptions hold true and Fisher's Exact Test when expected values in any cell [(row total*column total)/grand total] were less than or equal to 5. The comparison of continuous variables between the Vitamin K and Placebo groups were evaluated using the two-independent sample t-test for unequal variance. Genotypic frequencies of genetic polymorphisms assessed in this study were evaluated for adherence to Hardy-Weinberg using Chi-square analysis. For all statistical test, $p<\alpha=0.05$ was deemed to be statistically significant.

Intervention effectiveness was evaluated by computing change scores of the primary and secondary outcome measures (i.e: mean value in 6 months intervention period – mean value in 6 month pre-intervention period). Two sample independent t-tests with $\alpha=0.05$ were utilized to compare the intervention and control groups. Normality of distribution of the outcome measures was also evaluated by visual examination of Q-Q plots.

Intervention effectiveness was also evaluated by multivariate linear regression modelling of the outcome measure of anticoagulation control as a function of treatment allocation and pre-intervention outcome measure [i.e. % TTR during 6 month intervention period = Intercept + (Treatment Allocation)ß1+ (% TTR during 6 month pre-intervention period) ß2 + Ɛ]. The impact of potential confounding variables (see Introduction for the rationale for the inclusion of variables) on measures of anticoagulation control and intervention effectiveness was evaluated using multiple linear regression analysis [i.e. % TTR during 6 month intervention period = Intercept + (Treatment Allocation)ß1+ (% TTR during 6 month pre-intervention period) ß2 + (Potential Confounder)ß3 + Ɛ]

With respect to all linear regression models a least squares approach to model fitting was employed with the F statistics being utilized to evaluate the overall significance of the model (i.e: H_0: $\beta_1 = \beta_2 = \ldots = \beta_k = 0$). For all categorical explanatory variables, dummy variables were coded with number of variables being k-1 (where k= number of categories in the variables of interest). The significance of individual variables within the model will be evaluated using t-statistics of the individual variable slopes (H_0: $\beta_i = 0$). All parameters were reported as a point estimate along with their respective 95% confidence interval. Prior to model fitting, a matrix correlation analysis was utilized to evaluate relationship between the dependent variables and investigate for any potential co-linearity. In the event of significant co-linearity (i.e. $r > 0.9$) between two variables only one of the two variables was chosen and

that fact reported in the analysis. Once a model was fitted to the data, the standardized residuals were analyzed to examine for any potential outliers. In the event of an outlier being present ($3 \leq$ Standardized residual ≤ -3) the model was run both with and without the outlier to examine the effect on model parameters. If removal of an outlier did not alter the predictive variables (i.e. variable x_i was still a significant predictor) then the model was run with the outlier. Once the model was derived, the underlying assumptions of the model were tested. The normality assumption was evaluated by examining the dot-plot of the standardized residuals for Gaussian distribution around (mean = 0). The constant variance assumption (Homoscedasticity) was evaluated by visual inspection of the plot of standardized residuals against fitted Y values. Satisfaction of the homoscedasticity assumption would reveal that the variance of the residuals does not increase or decrease as Y increases (i.e. cone distribution pattern). Should the model show evidence of heteroscedasticity, a log or square root transformation of Y would be undertaken to reduce the heteroscedasticity and the fact reported in the results. The linearity assumption was confirmed by plotting the model residuals against each explanatory variable. If non-linear trends were observed, transformations would be undertaken of the associated variables to remove the non-linearities and the fact would be reported in the results.

Multiple linear regression modelling was also utilized to examine apriori any confounding effect of age and gender on total score received on the Anticoagulation Knowledge Assessment (AKA).

Frequency of adverse events between the two study arms was reported using descriptive measures.

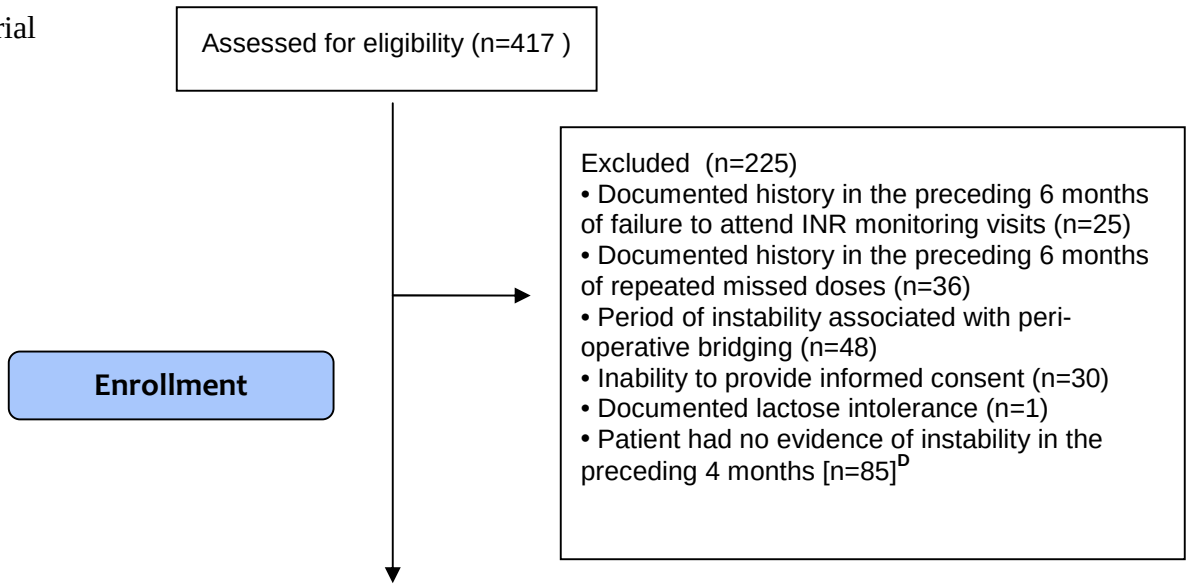
All statistical analysis was preformed using R version 2.13.1 (R Foundation for Statistical Computing).

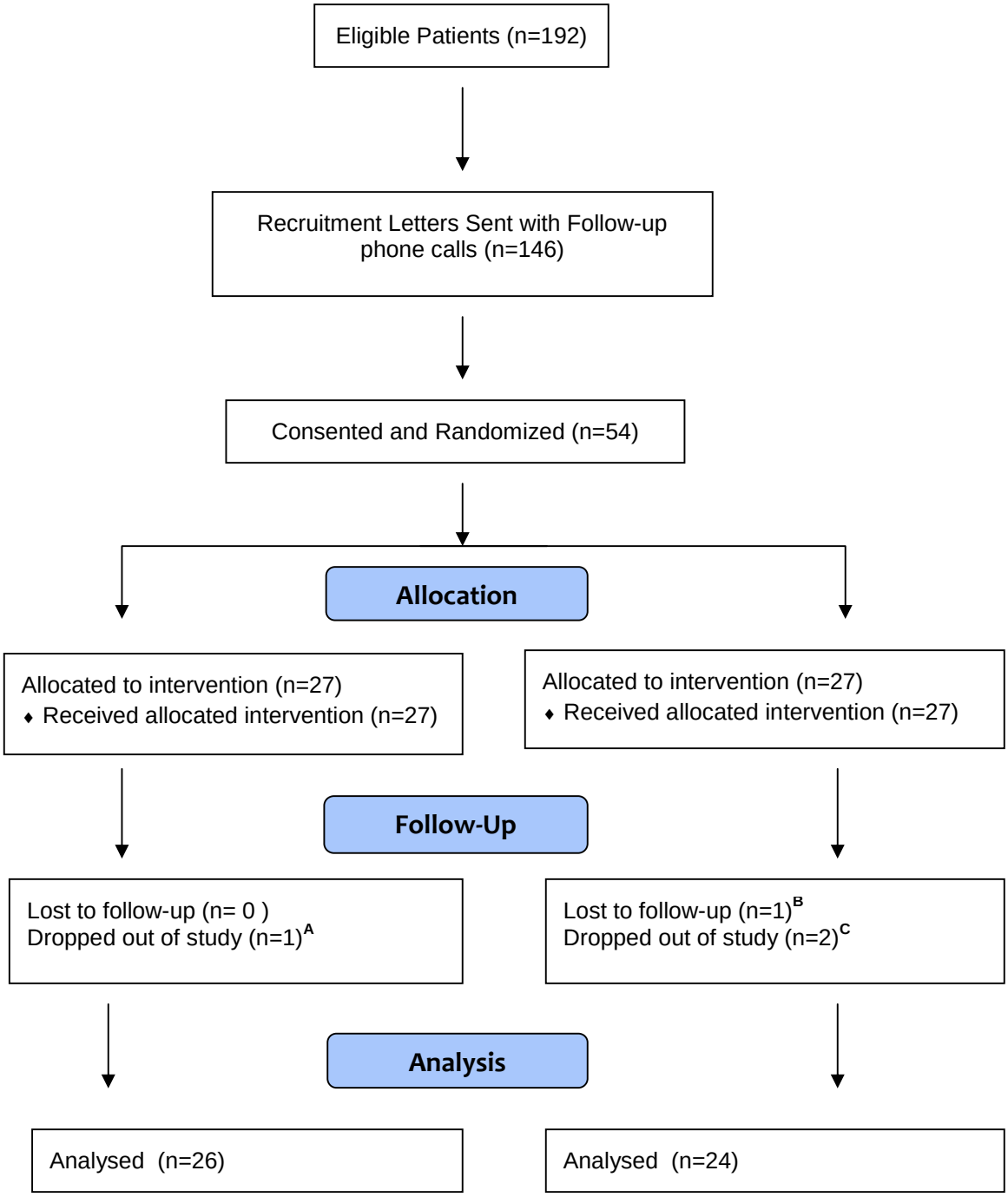
4. RESULTS

4.1 Recruitment

Recruitment for the LOCK [LOw Dose Supplementation to improve anticoagulation Control with Vitamin K] clinical trial occurred from January 2009 to August 2009 after approvals were received from the Ottawa Hospital Research Ethics Board in September 2008 and Health Canada in January 2009. Pending annual renewal of the study submitted in September 2009 [approval received November 2009] recruitment was held, with resumption from December 2009 to June 2010. Thus the total enrolment period for this clinical trail was 15 months. A search of the DAWN^{TM} Anticoagulation database of patients being managed by the Ottawa Hospital Anticoagulation Clinic revealed 417 patients who met the preliminary criteria of instability in this study [$\geq$ 3 dose changes or $\geq$ 3 INRs in the preceding 6 months]. Subsequent analysis of the aforementioned patients' records for conformity to the remaining inclusion/exclusion criteria for eligibility is summarized in Figure 1.

Figure 1: CONSORT diagram illustrating patients evaluated for eligibility in the clinical trial





[A] Patient dropped out at 11 days into study. Treatment crossover – patient switched anticoagulation management to family physician and received 500mg Vitamin K (0.5 of 1mg tab) daily from family physician.
[B] Patient dropped out 4 weeks into study. Failure to attend anticoagulation monitoring visits, anticoagulation thus transferred to family doctor
[C] Patient perceived reaction to study drug (n=1; dropped out 8 days into study). Patient felt could not comply with trial procedure due to prior commitments (n=1; dropped out 3 days into study)
[D] A post-hoc restriction was placed on the initial recruitment where patients who had achieved stable warfarin dose and associated therapeutic INRs in the preceding 4 months [but whose instability was exclusively within

the initial 2 months of the period examined] were excluded from solicitation [n=85]. The rationale being that these patients were currently stable and hence patient buy-in to participate in a trial at improving stability would likely yield poor results. Furthermore, anecdotal accounts from clinicians were that several of these patients had required an extensive amount of time to achieve stability and clinicians were concerned that enrolment in a trial that influenced dietary Vitamin K could shift these patients back into instability. Should recruitment goals not be met the plan was to contact these patients for recruitment as they fulfilled the study inclusion criteria

4.2 Baseline Demographics

Analysis of the intervention and control groups indicated no statistically significant difference between baseline clinical variables in the intervention and control arms of the study [Table 1]. Allele frequencies were also evaluated and found to be within Hardy-Weinberg equilibrium [Table 2].

Table 1: i) Baseline clinical characteristics of the study population enrolled, N=54 ii) Baseline measures of anticoagulation control prior to initiation of intervention, N=54

i)

Variable	**Vitamin K (N=27)**	**Placebo (N=27)**	**p-value**
Age, mean (std. dev), yr	60 (14)	59 (15)	0.8011[A]
Male, n (%)	15 (52)	14 (48)	0.7928[B]
Caucasian, n (%)	26 (96)	25 (92)	0.6179[C]
Height, mean (std. dev), in	66.3 (3.58)	67.4 (4.27)	0.3099[A]
Weight, mean (std. dev), lbs	179.7 (34.66)	187 (35.08)	0.4453[A]
Body Surface Area[D], BSA (std. dev)	1.94 (0.195)	2.00(0.228)	0.3036 [A]
Body Mass Index[E], BMI (std. dev)	28.96 (6.45)	28.84 (3.68)	0.9395 [A]
Number of Alcoholic drinks per week, n (%)			
0	13 (24)	12 (22)	0.8967[F]
1-4	9 (17)	8 (15)	
5-7	3 (6)	5 (9)	
8-10	1 (2)	0	
11-13	1 (2)	1(2)	
14 or more	0	1 (2)	
Indication for anticoagulation, n (%)			

Previous DVT/PE	23 (43)	24 (44)	1[G]
Atrial Fibrillation	4 (7)	3 (6)	
Patient reported Physical Activity, n (%)			
Much less than those of similar age	2 (4)	4 (7)	0.4545[H]
Less than those of similar age	8 (15)	7 (13)	
Similar to those of similar age	7 (13)	10 (19)	
More than those of similar age	4 (7)	6 (11)	
Much More than those of similar age	6 (11)	0	
Previous Major Bleed[O], n (%)			
Yes	1 (2)	1 (2)	1[I]
No	26 (48)	26 (48)	
Smoking Status, n (%)			
Current Users	2 (4)	7 (13)	0.1415[J]
Previous Users (have quit)	5 (9)	6 (11)	
Never Used	20 (37)	14 (26)	
Comorbidities, n (%)			
Active Cancer	1 (2)	4 (7)	0.3743[K]
Diabetes	1 (2)	2 (4)	1[L]
Hypertension	11 (20)	9 (17)	0.5004[M]
Inflammatory Bowel Disease	4 (7)	2 (4)	0.4949[N]
CYP2C9 polymorphism, n (%)			
Wildtype (*1*1)	17 (31)	17	0.2854[P]
2C9 *2 heterozygote (*1*2)	9 (17)	4 (7)	0.2556[Q]
2C9 *2 homozygote (*2*2)	1 (2)	0	0.5556[R]
2C9 *3 heterozygote (*1*3)	3 (6)	2 (4)	0.8604[S]
2C9 *3 homozygote (*3*3)	0	1 (2)	0.4444[T]
VKORC1 -1639 G>A polymorphism, n (%)			
GG homozygote	19 (35)	19 (35)	1[U]
GA heterozygote	8 (15)	5 (9)	0.3396[V]
AA homozygote	0	3 (6)	0.1179[W]
CYP4F2 1347 C>T polymorphism, n (%)			
CC homozygote	20 (37)	15 (28)	0.9574[X]
CT heterozygote	10 (19)	7 (13)	0.8866[Y]
TT homozygote	1 (2)	1 (2)	0.8519[Z]
Mean Number of Medications	3.5 (3.29)	3.09 (3.84)	0.6753[A]

per subject at baseline, mean (std. dev)			
Mean Number of Medications that Potentiate warfarin per subject at baseline, mean (std. dev)	0.444 (0.698)	0.296 (0.609)	0.4103[A]
Mean Number of Medications that Inhibit warfarin per subject at baseline, mean (std. dev)	0.074 (0.267)	0.185 (0.396)	0.2334 [A]
Mean Anticoagulation Knowledge Assessment Total Score, % (std. dev)	66 (12.59)	67 (17.46)	0.8103[A]

ii)

Variable	**Vitamin K (N=27)**	**Placebo (N=27)**	**p-value**
Mean Percent Time in Therapeutic Range in 6 month pre-intervention period, mean (std. dev), %	54.63 (16.00)	57.64(16.19)	0.4951[A]
Mean Standard Deviation INR in 6 month pre-intervention period, mean (std. dev)	0.76 (0.27)	0.73 (0.23)	0.6622[A]
Mean Number of INRs out of range (>3.0 or <2.0) in 6 month pre-intervention period, mean (std. dev)	9.56 (2.64)	10.27(2.37)	0.3033[A]
Mean Number of dose changes in 6 month pre-intervention period, mean (std. dev)	6.48 (4.46)	6.68 (3.56)	0.8562[A]

A : 2 sample t-test for unequal variance, 2-sided p-value < 0.05 significant
B, M : chi-square analysis, 2 sided p<0.05 significant
C: Fisher's Exact Test, 2 sided p<0.05 significant, Caucasian vs non-Caucasian
D: BSA = $[\{\text{Height [cm]} \times \text{Weight[kg]}\}/3600]^{1/2}$
E: BMI = $\text{weight[kg]}/\text{height[m]}^2$
F: chi-square analysis [rxc = No drinks, 1-4 drinks, 5-7 drinks, > 8-10 drinks], df=3, p<0.05 significant
G: Fisher's Exact Test, 2 sided p<0.05 significant. Mid P Exact 2-sided p-value 0.7101
H: chi-square analysis [rxc = Less, Similar, More], df=2, p<0.05 significant
I: Fisher's Exact Test, 2 sided p<0.05 significant. Mid P Exact 2-sided p-value 0.6179
J: Fisher's Exact Test. Non-smoker [Never Used and Previous Smoker] vs Smoker, 2 sided p<0.05 significant. Mid-P Exact 2 sided p-value 0.08292
K: Fisher's Exact Test, 2 sided p<0.05 significant. Mid P Exact 2-sided p-value 0.2153
L: Fisher's Exact Test, 2 sided p<0.05 significant. Mid P Exact 2-sided p-value 0.6393
N: Fisher's Exact Test, 2 sided p<0.05 significant. Mid P Exact 2-sided p-value 0.3070

O: Major Bleed Defined according to ISTH criteria as : i) Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, or pericardial, or intramuscular with compartment syndrome, and/or ii) Bleeding causing a fall in haemoglobin level of 20 g/L or more, or leading to transfusion of two or more units of whole blood or red cells. For subjects in this trial there were two pre-intervention major bleeds. One subject had an intraocular bleed and a second subject had a GI bleed requiring hospitalization and transfusion of packed red cells.
P: Chi-square analysis (Wildtype vs Non-wildtype), 2-sided $p<0.05$ significant
Q: Chi-square analysis (CYP2C9*1*2 vs non CYP2C9*1*2), 2-sided $p<0.05$ significant
R, S: Chi-square analysis (CYP2C9*2*2 vs non CYP2C9*2*2; CYP2C9*1*3 vs non CYP2C9*1*3). Mid P exact 2-sided P value, Fisher's Exact 2 sided p-value > 0.9999
T: Chi-square analysis (CYP2C9*3*3 vs non CYP2C9*3*3). Mid P exact 2-sided P value, Fisher's Exact 2 sided p-value 0.8889
U: Chi-square analysis (VKORC1 GG vs Non- VKORC1 GG), 2-sided $p<0.05$ significant
V: Chi-square analysis (VKORC1 GA vs Non- VKORC1 GA), 2-sided $p<0.05$ significant
W: Chi-square analysis (VKORC1 AA vs Non- VKORC1 AA). Mid P exact 2-sided P value, Fisher's Exact 2 sided p-value 0.2358
X: Chi-square analysis (CYP4F2 CC vs Non- CYP4F2 CC), 2-sided $p<0.05$ significant
Y: Chi-square analysis (CYP4F2 CT vs Non- CYP4F2 CT), 2-sided $p<0.05$ significant
Z: Chi-square analysis (CYP4F2 TT vs Non- CYP4F2 TT). Mid P exact 2-sided P value, Fisher's Exact 2 sided p-value > 0.9999

Table 2: Genotypic frequencies of polymorphisms in warfarin and vitamin K metabolism evaluated. P-values reported for hypothesis testing of adherence of population genotypic frequencies to Hardy Weinberg Equilibrium. [N= 54 subjects]

Polymorphism		**p-value**
CYP2C9 polymorphism, n (%)		0.8507^{A}, 0.1695^{B}
Wildtype (*1*1)	34 (63)	
2C9 *2 heterozygote (*1*2)	13 (24)	
2C9 *2 homozygote (*2*2)	1 (2)	
2C9 *3 heterozygote (*1*3)	5 (9)	
2C9 *3 homozygote (*3*3)	1 (2)	
VKORC1 -1639 G>A polymorphism, n (%)		0.2123^{C}
GG homozygote	38 (70)	
GA heterozygote	13 (24)	
AA homozygote	3 (6)	
CYP4F2 1347 C>T polymorphism, n (%)		0.9711^{D}
CC homozygote	35 (65)	
CT heterozygote	17 (31)	
TT homozygote	2 (4)	

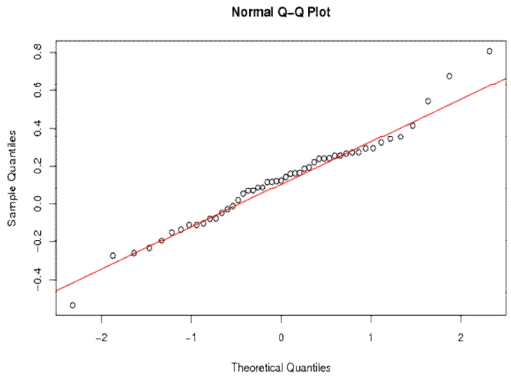
A: CYP*2 Polymorphisms (*1*1,*1*2,*2*2). Hardy-Weinberg Equilibrium (Chi-Square), df=1
B: CYP*3 Polymorphisms (*1*1,*1*3,*3*3). Hardy-Weinberg Equilibrium (Chi-Square), df=1
C: VKORC1 -1639 G>A polymorphism (GG, GA, AA). Hardy-Weinberg Equilibrium (Chi-Square), df=1
D: CYP4F2 1347 C>T polymorphism (CC, CT, TT). Hardy-Weinberg Equilibrium (Chi-Square), df=1

4.3 Normality Assessment of the primary and secondary outcome measures of anticoagulation control

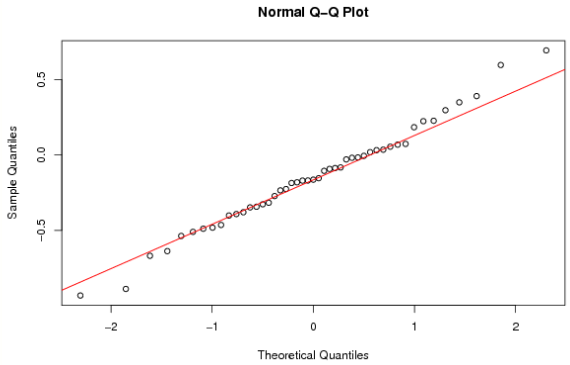
Q-Q plots for each of the primary and secondary outcome measures of anticoagulation control [change score of : % TTR, Standard deviation of INRs, Number of INRs out of range, and Number of Dose changes] are presented in Figure 1. Visual inspection of the Q-Q plots shows a significant degree of linearity following the line y=x; thereby suggestive of normality in the distribution of the underlying variable.

Figure 2: Normal Q-Q plots to evaluate normality of distributions of outcome variables.

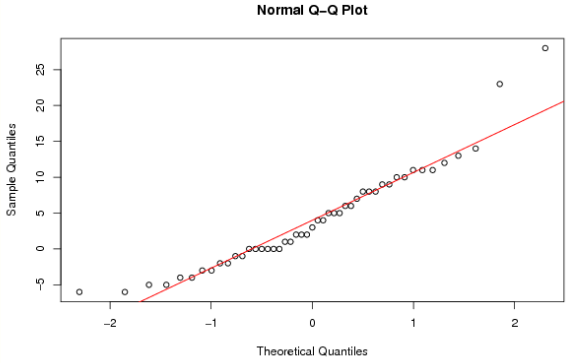
a) Change Score of % time in therapeutic range [Change % TTR] between 6 month intervention period and 6 month pre-intervention period [N=50]. Mean±STDEV: 9.31%±20.87%. Median: 12.31



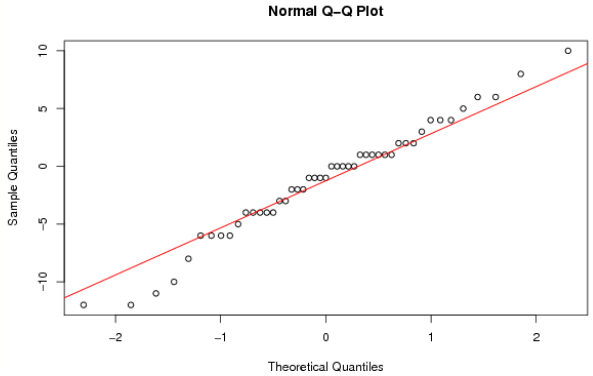
b) Change score of Standard deviation of INRs between 6 month intervention period and 6 month pre-intervention period [N=50]. Mean±STDEV: -0.150±0.341. Median: -0.164



c) Change score of Number of out of range INRs [>3.0 or < 2.0] INRs between 6 month intervention period and 6 month pre-intervention period [N=50]. Mean±STDEV: 4.17±7.15 Median: 3



d) Change score of Number of dose changes between 6 month intervention period and 6 month pre-intervention period [N=50]. Mean±STDEV: -1.19±4.94. Median: -1



4.4 Intervention Effectiveness

Change scores (between the 6 month intervention period and the preceding 6-month pre-intervention period) of the primary and secondary measures of anticoagulation control were calculated and summarized for both the Vitamin K and Placebo groups [See Table 3]. A statistically significant difference was observed in the mean change score of standard deviation of INRs. Patients allocated to the Vitamin K group demonstrating an increased reduction in INR standard deviation between the pre-intervention and intervention period (absolute difference -0.213 relative to placebo group; p=0.0261).

Table 3: Primary and Secondary measures of anticoagulation control evaluated in the study for N=50 patients enrolled and followed.

Anticoagulation Control Measures	**Vitamin K (N=26)**	**Placebo (N=24)**	**P-value [B]**
Mean Change Score [A] of % Time in Therapeutic Range, mean (std. dev.), %	9.40 (19.15)	9.22 (22.81)	0.9761
Mean Change Score [A] of Standard Deviation INR, mean (std. dev.)	-0.259 (0.307)	-0.046 (0.345)	**0.0261**
Mean Change Score [A] of Number of INRs out of range (>3.0 or <2.0), mean (std. dev.)	3.17 (5.715)	5 (8.288)	0.3726
Mean Change Score [A] of Number of dose changes, mean (std. dev.)	-1.57 (5.026)	-0.833 (4.949)	0.6040

[A] Mean Change score (Outcome measure in 6 month intervention period – Outcome measure in 6 month pre-intervention period)
[B] 2-sample t-test for independent samples with unequal variance, two tailed p-value<0.05 significant

4.5 Regression Modeling of Measures of Anticoagulation Control as a function of Treatment Allocation

Table 4.5.1 Linear Regression Model of Percent Time in Therapeutic Range during study (Y) as a function of Treatment Allocation

i)

Regression Statistics	Value
R Square	0.055
Adjusted R Square	0.011
Standard Error	0.170
F statistic	1.2459
p-value	0.298

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	0.5246	5.5977	0.0000	0.3356	0.7136
Vitamin K Group	-0.0058	-0.1153	0.9087	-0.1074	0.0957
% TTR pre study	0.2393	1.5629	0.1254	-0.0695	0.5481

Table 4.5.2 Linear Regression Model of Standard Deviation of INRs during the intervention period (Y) as a function of Treatment Allocation

i)

Regression Statistics	Value
R Square	0.197
Adjusted R Square	0.159
Standard Error	0.253
F statistic	5.2639
p-value	0.009

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	0.5875	4.7068	0.0000	0.3358	0.8392
Vitamin K Group	-0.2277	-3.0471	0.0039	-0.3785	-0.0770
STDEV INRS Pre-study	0.1635	1.0900	0.2818	-0.1390	0.4661

Table 4.5.3 Linear Regression Model of Number of INRs out of Range during the intervention period (Y) as a function of Treatment Allocation

i)

Regression Statistics	Value
R Square	0.031
Adjusted R Square	-0.015
Standard Error	6.439
F statistic	0.678
p-value	0.513

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	8.3477	3.8346	0.0004	3.9544	12.7410
Vitamin K Group	-0.6027	-0.3130	0.7558	-4.4885	3.2831
# INRs out of Range Prestudy	0.3214	1.1418	0.2600	-0.2467	0.8896

Regression Parameter	With Outlier[A]	Without Outlier	% Change
R Square[C]	0.132	0.129	-2.65
Standard Error	7.266	7.346	1.11
Intercept	6.8589	8.3477	21.71
Vitamin K Group	-1.7013	-0.6027	-64.57
# INRs out of Range Prestudy[B]	0.7140	0.3214	-54.98

[A]Outlier (N =1 patient allocated to the placebo group and who had 16 INRs out of range during the pre-study period , Standardized residual of Predicted Y = 3.93)

[B] P-value of regression coefficient with outliers (p=0.0188) and without outlier (p=0.2600)

[C] F statistic and p-value of regression model with outlier (F=3.272, p=0.048). F statistic and p-value of regression model without outlier (F=0.678, p=0.513)

Table 4.5.4 Linear Regression Model of Dose Changes during the intervention period (Y) as a function of Treatment Allocation

i)

Regression Statistics	Value
R Square	0.019
Adjusted R Square	-0.027
Standard Error	3.448
F statistic	0.417
p-value	0.371

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	4.4884	4.0224	0.0002	2.2365	6.7404
Vitamin K Group	-0.1650	-0.1604	0.8734	-2.2420	1.9119
# Dose Changes Prestudy	0.1192	0.9051	0.3706	-0.1466	0.3851

Regression Parameter	**With Outlier[A]**	**Without Outlier**	**% Change**
R Square[C]	0.080	0.0195	-75.79
Standard Error	4.098	3.4479	-15.87
Intercept	4.0994	4.4884	9.49
Treatment	-0.8292	-0.1650	-80.10
# Dose Changes Prestudy[B]	0.2737	0.1192	-56.44

[A]Outlier (N =1 patient allocated to the placebo group and who had 14 dose changes during the pre-study period, Standardized residual of Predicted Y = 3.49)
[B] P-value of regression coefficient with outliers (p=0.076) and without outlier (p=0.371)
[C]F statistic and p-value of regression model with outlier (F=1.880, p=0.165). F statistic and p-value of regression model without outlier (F=0.417, p=0.662)

4.6 Evaluation of the Effects of Clinical and Demographic Variables on Measures of Anticoagulation Control and Intervention Effectiveness

Table 4.6.1 Effect of Age (at enrolment) on measures of anticoagulation control during study period

a. Association between Time in Therapeutic Range during the intervention period and Age (at enrolment) i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	**Value**
R Square	0.056
Adjusted R Square	-0.012
Standard Error	0.172
F statistic	0.8278
p-value	0.486

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	0.5423	4.323	0.000	0.2892	0.7955
Vitamin K Group	-0.0060	-0.1171	0.907	-0.1087	0.0968
Age	-0.0004	-0.2161	0.830	-0.0044	0.0036
% TTR pre study	0.2521	1.521	0.136	-0.0825	0.5867

b. Association between Standard Deviation of INRs during intervention period and Age (at enrolment) i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.242
Adjusted R Square	0.188
Standard Error	0.249
F statistic	4.468
p-value	0.008

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	0.8920	3.911	0.000	0.4317	1.352
Vitamin K Group	-0.2325	-3.163	0.003	-0.3809	-0.0841
STDEV INRS Pre-study	0.1004	0.6571	0.515	-0.2079	0.4087
Age (at Enrolment)	-0.0044	-1.584	0.121	-0.0099	0.0012

c. Association between Number of INRs out of range during intervention period and Age (at enrolment) i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.147
Adjusted R Square	0.086
Standard Error	7.289
F statistic	2.4099
p-value	0.080

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	11.5506	1.9217	0.0615	-0.5796	23.6809
Vitamin K Group	-1.7664	-0.8205	0.4166	-6.1111	2.5782
# INRs out of Range Prestudy	0.6279	2.0238	0.0494	0.0018	1.2540
Age (at Enrollment)	-0.0703	-0.8526	0.3987	-0.2367	0.0961

d. Association between Number of dose changes during intervention period and Age (at enrolment) i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	***Value***
R Square	0.092
Adjusted R Square	0.027
Standard Error	4.120
F statistic	1.419
p-value	0.250

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	6.3544	1.9001	0.0643	-0.3944	13.1033
Vitamin K Group	-0.8637	-0.7096	0.4818	-3.3198	1.5924
# Dose Changes Prestudy	0.2369	1.4841	0.1453	-0.0852	0.5590
Age (at Enrollment)	-0.0341	-0.7348	0.4665	-0.1278	0.0596

Table 4.6.2 Effect of Gender on measures of anticoagulation control during study period

a. Association between Time in Therapeutic Range during intervention period and Gender i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.062
Adjusted R Square	-0.005
Standard Error	0.172
F statistic	0.9261
p-value	0.437

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	0.5099	5.209	0.000	0.3123	0.7075
Vitamin K Group	-0.0071	-0.1400	0.889	-0.1096	0.0954
Female	0.0289	0.5707	0.571	-0.0734	0.1312
% TTR pre study	0.2397	1.553	0.128	-0.0718	0.5511

b. Association between Standard Deviation of INRs during intervention period and Gender i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.200
Adjusted R Square	0.143
Standard Error	0.256
F statistic	3.5009
p-value	0.024

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	0.5667	4.1835	0.0001	0.2933	0.8400
Vitamin K Group	-0.2291	-3.0335	0.0041	-0.3816	-0.0767
STDEV INRS Pre-study	0.1700	1.1165	0.2706	-0.1373	0.4773
Female	0.0319	0.4199	0.6767	-0.1213	0.1851

c. Association between Number of INRs out of range during intervention period and Gender i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.035
Adjusted R Square	-0.036
Standard Error	6.505
F statistic	0.4929
p-value	0.689

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	8.7435	3.6047	0.0008	3.8450	13.6421
Vitamin K Group	-0.5491	-0.2816	0.7797	-4.4876	3.3893
# INRs out of Range Prestudy	0.3156	1.1082	0.2743	-0.2596	0.8908
Female	-0.7535	-0.3870	0.7008	-4.6857	3.1788

Regression Parameter	**With Outlier[A]**	**Without Outlier**	**% Change**
R Square[C]	0.1326	0.0348	-73.75
Standard Error	7.3493	6.5053	-11.48
Intercept	6.6882	8.7435	30.73
Vitamin K Group	-1.7171	-0.5491	-68.02
# INRs out of Range Prestudy[B]	0.7135	0.3156	-55.76
Female	0.3481	-0.7535	-316.43

[A]Outlier (N =1 patient with Female gender, Standardized residual of Predicted Y = 3.61)
[B] P-value of regression coefficient with outliers (p=0.0203) and without outlier (p=0.2743)
[C] F statistic and p-value of regression model with outlier (F=2.14, p=0.109). F statistic and p-value of regression model without outlier (F=0.4929, p=0.689)

d. Association between Number of dose changes during intervention period and Gender

i) Regression Statistics with F-Test for overall model significance(H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.082
Adjusted R Square	0.016
Standard Error	4.144
F statistic	1.2432
p-value	0.3062

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	3.9552	2.6786	0.0105	0.9753	6.9351
Treatment	-0.8420	-0.6877	0.4954	-3.3130	1.6290
# Dose Changes Prestudy	0.2742	1.7989	0.0792	-0.0334	0.5818
Female	0.2816	0.2299	0.8193	-2.1897	2.7528

Regression Parameter	**With Outlier[A]**	**Without Outlier**	**% Change**
R Square[C]	0.0816	0.0237	-70.95
Standard Error	4.1440	3.4821	-15.97
Intercept	3.9552	4.7196	19.33
Vitamin K Group	-0.8420	-0.1344	-84.04
# Dose Changes Prestudy[B]	0.2742	0.1160	-57.71
Gender	0.2816	-0.4393	-256.01

[A]Outlier (N =1 patient with Female gender, Standardized residual of Predicted Y = 3.58)
[B] P-value of regression coefficient with outliers (p=0.0792) and without outlier (p=0.3892)
[C] F statistic and p-value of regression model with outlier (F=1.2432, p=0.3062). F statistic and p-value of regression model without outlier (F=0.3317, p=0.802)

Table 4.6.3 Effect of BMI on measures of anticoagulation control during study period

a. Association between Time in Therapeutic Range during intervention period and Body Mass Index (BMI) i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes(H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.086
Adjusted R Square	0.021
Standard Error	0.169
F statistic	1.324
p-value	0.279

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	0.357	2.140	0.038	0.0204	0.6945
Vitamin K Group	-0.01	-0.2607	0.796	-0.115	0.0887

% TTR pre study	0.24	1.576	0.122	-0.0673	0.5475
BMI	0.006	1.206	0.235	-0.0039	0.0156

b. Association between Standard Deviation of INRs during intervention period and Body Mass Index (BMI) i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	***Value***
R Square	0.211
Adjusted R Square	0.155
Standard Error	0.254
F statistic	3.7483
p-value	0.018

ii)

	Coefficients	***t Stat***	***P-value***	***Lower 95%***	***Upper 95%***
Intercept	0.7886	3.0240	0.0042	0.2623	1.3149
Vitamin K Group	-0.2197	-2.9096	0.0058	-0.3720	-0.0673
STDEV INRS Pre-study	0.1418	0.9300	0.3577	-0.1659	0.4495
BMI	-0.0064	-0.8790	0.3844	-0.0212	0.0084

c. Association between Number of INRs out of range during intervention period and Body Mass Index (BMI) i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	***Value***
R Square	0.065
Adjusted R Square	-0.004
Standard Error	6.403
F statistic	0.9485
p-value	0.426

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	14.6358	2.6070	0.0127	3.2981	25.9735
Vitamin K Group	-0.3761	-0.1955	0.8460	-4.2613	3.5091
# INRs out of Range Prestudy	0.3503	1.2468	0.2196	-0.2171	0.9177
BMI	-0.2242	-1.2140	0.2317	-0.5971	0.1488

Regression Parameter	**With Outlier[A]**	**Without Outlier**	**% Change**
R Square[C]	0.1795	0.0649	-63.84
Standard Error	7.1481	6.4031	-10.42
Intercept	15.8693	14.6358	-7.77
Vitamin K Group	-1.3007	-0.3761	-71.09
# INRs out of Range Prestudy[B]	0.7263	0.3503	-51.77
BMI	-0.3174	-0.2242	-29.37

[A]Outlier (N =1 patient with BMI of 24.27, Standardized residual of Predicted Y = 3.30)
[B] P-value of regression coefficient with outliers (p=0.015) and without outlier (p=0.2196)
[C] F statistic and p-value of regression model with outlier (F=3.0619, p=0.0384). F statistic and p-value of regression model without outlier (F=0.9485, p=0.4261)

d. Association between Number of dose changes during intervention period and Body Mass Index (BMI) i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.127
Adjusted R Square	0.065
Standard Error	4.040
F statistic	2.037
p-value	0.123

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	8.8959	2.5730	0.0137	1.9185	15.8734
Treatment	-0.6101	-0.5078	0.6142	-3.0347	1.8145
# Dose Changes Prestudy	0.2999	2.0045	0.0515	-0.0020	0.6019
BMI	-0.1737	-1.4978	0.1417	-0.4077	0.0603

Table 4.6.4 Effect of the Number of Self-reported Drinks per week at baseline on measures of anticoagulation control during study period

a. Association between Time in Therapeutic Range during intervention period and Number of Self-reported Drinks per week at baseline i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.117
Adjusted R Square	0.031
Standard Error	0.168
F statistic	1.3566
p-value	0.266

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	0.5681	5.835	0.000	0.3715	0.7647
Vitamin K Group	-0.0097	-0.195	0.847	-0.1109	0.0914
% TTR pre study	0.2358	1.555	0.128	-0.0705	0.5421
1-4 Drinks per week	-0.0493	-0.864	0.393	-0.1645	0.066
$\geq$ 5 drinks per week	-0.1087	-1.676	0.101	-0.2396	0.0223

b. Association between Standard deviation of INRs during intervention period and Number of Self-reported Drinks per week at baseline i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.317
Adjusted R Square	0.250
Standard Error	0.239
F statistic	4.758
p-value	0.003

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	0.4609	3.5760	0.0009	0.2006	0.7212
Vitamin K Group	-0.2228	-3.1425	0.0031	-0.3660	-0.0796
STDEV INRS Pre-study	0.1968	1.3730	0.1772	-0.0927	0.4864
1-4 Drinks per week	0.1508	1.8425	0.0726	-0.0145	0.3162
≥ 5 drinks per week	0.2295	2.4930	0.0168	0.0436	0.4155

c. Association between Number of INRs out of range during intervention period and Number of Self-reported Drinks per week at baseline i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.258
Adjusted R Square	0.186
Standard Error	6.878
F statistic	3.5713
p-value	0.014

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	4.5820	1.8358	0.0737	-0.4587	9.6227
Vitamin K Group	-1.4255	-0.6988	0.4886	-5.5451	2.6941
# INRs out of Range Prestudy	0.6694	2.4137	0.0203	0.1093	1.2295
1-4 Drinks per week	2.8268	1.2136	0.2318	-1.8772	7.5307
≥ 5 drinks per week	6.9692	2.6279	0.0120	1.6135	12.3249

Regression Parameter	**With Outlier[A]**	**Without Outlier**	**% Change**
R Square[E]	0.2580	0.2770	7.36
Standard Error	6.8780	6.2980	-8.43
Intercept	4.5820	3.4462	-24.79
Vitamin K Group	-1.4255	-0.7277	-48.95
# INRs out of Range Pre-study[B]	0.6694	0.7963	18.95
1-4 Drinks per week[C]	2.8268	2.7530	-2.61
≥ 5 drinks per week[D]	6.9692	4.9266	-29.31

[A]Outlier (N =1 patient allocated to the placebo group with 3 INRs out of range during the pre-study period and consumption of ≥5drinks per week, Standardized residual of Predicted Y = 3.30)

[B] P-value of regression coefficient with outliers (p=0.023) and without outlier (p=0.0036)
[C] P-value of regression coefficient with outliers (p=0.2318) and without outlier (p=0.2042)
[D] P-value of regression coefficient with outliers (p=0.0120) and without outlier (p=0.0579)
[E] F statistic and p-value of regression model with outlier (F=3.57, p=0.014). F statistic and p-value of regression model without outlier (F=3.83, p=0.010)

d. Association between Number of dose changes during intervention period and Number of Self-reported Drinks per week at baseline i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.321
Adjusted R Square	0.255
Standard Error	3.605
F statistic	4.8545
p-value	0.003

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	2.0156	1.5487	0.1291	-0.6128	4.6439
Vitamin K Group	-0.6567	-0.6143	0.5424	-2.8159	1.5024
# Dose Changes Prestudy	0.2814	2.1212	0.0400	0.0135	0.5493
1-4 Drinks per week	2.5170	2.0624	0.0455	0.0522	4.9817
≥ 5 drinks per week	5.1899	3.7395	0.0006	2.3871	7.9927

Table 4.6.5 Effect of the Indication of Anticoagulation on measures of anticoagulation control during study period

a. Association between Time in Therapeutic Range during intervention period and Indication for Anticoagulation i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.056
Adjusted R Square	-0.011
Standard Error	0.172
F statistic	0.8302
p-value	0.485

ii)

	Coefficients	**t Stat**	**P-value**	**Lower 95%**	**Upper 95%**
Intercept	0.5251	5.539	0.000	0.3338	0.7163
Vitamin K Group	-0.0056	-0.1099	0.913	-0.1084	0.0972
% TTR pre study	0.2416	1.557	0.127	-0.0715	0.5546
Atrial Fibrillation	-0.0209	-0.2313	0.818	-0.2030	0.1612

b. Association between Standard deviation of INRs during intervention period and Indication for Anticoagulation i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.228
Adjusted R Square	0.173
Standard Error	0.251
F statistic	4.129
p-value	0.012

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	0.5808	4.6859	0.0000	0.3306	0.8309
Vitamin K Group	-0.2263	-3.0519	0.0039	-0.3760	-0.0767
STDEV INRS Pre-study	0.1914	1.2730	0.2100	-0.1120	0.4949
A.fib Indication for Warfarin	-0.1727	-1.3002	0.2006	-0.4407	0.0953

Regression Parameter	**With Outliers[A]**	**Without Outliers**	**% Change**
R Square[C]	0.228	0.230	0.78
Adjusted R Square	0.173	0.172	-0.50
Standard Error	0.251	0.257	2.24

Intercept	0.5808	0.5749	-1.01
Vitamin K Group[B]	-0.2263	-0.2364	4.46
STDEV INRS Pre-study	0.1914	0.2058	7.50
A.fib Indication for Warfarin	-0.1727	-0.1160	-32.84

[A]Outlier (N=2 patients both with Atrial Fibrilation as indication for anticoagulation, Standardized Residuals of Predicted Y are 3.18 and 3.44 respectively).
[B] P-value of regression coefficient with outliers (p=0.004) and without outlier (p=0.005)
[C] F statistic and p-value of regression model with outlier (F=4.129, p=0.012). F statistic and p-value of regression model without outlier (F=3.97, p=0.014)

c. Association between Number of INRs out of range during intervention period and Indication for Anticoagulation i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
Multiple R	0.1872
R Square	0.0350
Adjusted R Square	-0.0356
Standard Error	6.5045
F statistic	0.4963
p-value	0.6869

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	8.5360	3.7954	0.0005	3.9940	13.0780
Vitamin K Group	-0.5916	-0.3041	0.7626	-4.5200	3.3369
# INRs out of Range Prestudy	0.3101	1.0848	0.2843	-0.2671	0.8873
A.fib Indication for Warfarin	-1.3680	-0.3995	0.6916	-8.2837	5.5476

Regression Parameter	**With Outlier[A]**	**Without Outlier**	**% Change**
R Square[C]	0.1348	0.0350	-74.00
Standard Error	7.3402	6.5045	-11.38
Intercept	7.0511	8.5360	21.06
Vitamin K Group	-1.6897	-0.5916	-64.99
# INRs out of Range Pre-study[B]	0.7023	0.3101	-55.85
A.fib Indication for Warfarin	-1.3934	-1.3680	-1.82

[A]Outlier (N=1 with Previous VTE as indication for anticoagulation, Standardized Residual of Predicted Y = 3.96).
[B]P-value of regression coefficient with outliers (p=0.0023) and without outlier (p=0.284)

[C] F statistic and p-value of regression model with outlier (F=2.18, p=0.105). F statistic and p-value of regression model without outlier (F=0.496, p=0.687)

d. Association between Number of dose changes during intervention period and Indication for Anticoagulation i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.020
Adjusted R Square	-0.053
Standard Error	3.504
F statistic	1.4247
p-value	0.2490

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	4.2511	3.1619	0.0029	1.5378	6.9643
Vitamin K Group	-0.8170	-0.6718	0.5054	-3.2711	1.6371
# Dose Changes Prestudy	0.2711	1.7885	0.0809	-0.0348	0.5769
A.fib Indication for Warfarin	-1.6045	-0.7440	0.4610	-5.9563	2.7474

Regression Parameter	**With Outlier[A]**	**Without Outlier**	**% Change**
R Square[C]	0.092	0.031	-66.30
Standard Error	4.120	3.468	-14.94
Intercept	4.2511	4.6084	13.31
Vitamin K Group	-0.8170	-0.1595	-72.36
# Dose Changes Prestudy[B]	0.2711	0.1181	-68.49
A.fib Indication for Warfarin	-1.6045	-1.2964	-21.51

[A]Outliers (N=1 Outliers with Previous VTE as indication for anticoagulation, Standardized Residuals of Predicted Y = 3.09).
[B]P-value of regression coefficient with outliers (p=0.08) and without outlier (p=0.89)
[C] F statistic and p-value of regression model with outlier (F=1.42, p=0.249). F statistic and p-value of regression model without outlier (F=0.444, p=0.723)

Table 4.6.6 Effect of Smoking Status on measures of anticoagulation control during study period

a. Association between Time in Therapeutic Range during intervention period and Smoking Status i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
Multiple R	0.288
R Square	0.083
Adjusted R Square	0.017
Standard Error	0.170
F statistic	1.263
p-value	0.299

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	0.5706	5.602	0.000	0.3650	0.7761
Vitamin K Group	-0.0220	-0.4212	0.676	-0.1273	0.0833
% TTR pre study	0.1974	1.257	0.216	-0.1196	0.5143
Current Smoker	-0.0759	-1.132	0.264	-0.2113	0.0594

b. Association between Standard Deviation of INRs during intervention period and Smoking Status i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.255
Adjusted R Square	0.202
Standard Error	0.247
F statistic	4.802
p-value	0.006

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	0.5797	4.7643	0.0000	0.3341	0.8252
Vitamin K Group	-0.1925	-2.5560	0.0143	-0.3446	-0.0405
STDEV INRS Pre-study	0.1059	0.7083	0.4826	-0.1959	0.4077
Current Smoker	0.1765	1.8200	0.0759	-0.0192	0.3721

c. Association between Number of INRs out of range during intervention period and Smoking Status i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.197
Adjusted R Square	0.139
Standard Error	7.073
F statistic	3.4281
p-value	0.025

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	5.9331	2.4718	0.0176	1.0891	10.7771
Vitamin K Group	-0.6781	-0.3138	0.7552	-5.0385	3.6823
# INRs out of Range Prestudy	0.6295	2.1830	0.0347	0.0475	1.2114
Current Smoker	5.0583	1.8380	0.0731	-0.4957	10.6124

Regression Coefficient	**With Outlier[A]**	**Without Outlier**	**% Change**
R Square[D]	0.197	0.202	2.54
Standard Error	7.073	7.128	0.78
Intercept	5.9331	5.3827	-9.28
Treatment	-0.6781	-0.5059	-25.40
# INRs out of Range Prestudy[B]	0.6295	0.7235	14.94
Smoking Status (Smoker)[C]	5.0583	4.8494	-4.13

[A]Outliers (N=1 Outliers with 18 INRs out of range in the pre-study period and non-smoker, Standardized Residuals of Predicted Y = -3.23).
[B]P-value of regression coefficient with outliers (p=0.035) and without outlier (p=0.035)
[C] P-value of regression coefficient with outliers (p=0.073) and without outlier (p=0.090)
[D] F statistic and p-value of regression model with outlier (F=3.43, p=0.025). F statistic and p-value of regression model without outlier (F=3.45, p=0.025)

d. Association between Number of dose changes during intervention period and Smoking Status i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
Multiple R	0.383
R Square	0.146
Adjusted R Square	0.085
Standard Error	3.995
F statistic	2.402
p-value	0.081

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	3.5120	2.6421	0.0115	0.8295	6.1946
Vitamin K Group	-0.2685	-0.2202	0.8268	-2.7295	2.1925
# Dose Changes Prestudy	0.2404	1.6236	0.1119	-0.0584	0.5393
Current Smoker	2.7887	1.8030	0.0786	-0.3326	5.9101

Regression Coefficient	**With Outlier[A]**	**Without Outlier**	**% Change**
R Square[D]	0.146	0.140	-4.11
Standard Error	3.995	4.043	1.20
Intercept	3.5120	3.5037	-0.24
Treatment	-0.2685	-0.2657	-1.03
# INRs out of Range Prestudy[B]	0.2404	0.2418	0.56
Smoking Status (Smoker)[C]	2.7887	2.7860	-0.10

[A]Outliers (N=1 Outliers with 20 dose changes in the pre-study period and non-smoker, Standardized Residuals of Predicted Y = -3.30).
[B]P-value of regression coefficient with outliers (p=0.112) and without outlier (p=0.171)
[C] P-value of regression coefficient with outliers (p=0.079) and without outlier (p=0.084)
[D] F statistic and p-value of regression model with outlier (F=2.40, p=0.08). F statistic and p-value of regression model without outlier (F=2.22, p=0.100)

Table 4.6.7 Effect of Physical Activity on measures of anticoagulation control during study period

a. Association between Time in Therapeutic Range during intervention period and Self-reported Physical Activity Level. i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.180
Adjusted R Square	0.100
Standard Error	0.162
F statistic	2.249
p-value	0.080

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	0.6341	5.8237	0.000	0.4142	0.8541
Vitamin K Group	0.0084	0.1695	0.866	-0.0912	0.1079
% TTR pre study	0.177	1.1474	0.258	-0.1346	0.4887
Less Activity than those of Similar Age	-0.1457	-2.422	0.020	-0.2672	-0.0242
More Activity than those of Similar Age	-0.0646	-0.935	0.355	-0.2041	0.0749

b. Association between Standard Deviation during intervention period and Self-reported Physical Activity Level i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.315
Adjusted R Square	0.248

Standard Error	0.239
F statistic	4.718
p-value	0.003

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	0.5079	4.1701	0.0002	0.2619	0.7538
Vitamin K Group	-0.2690	-3.6949	0.0006	-0.4160	-0.1220
STDEV INRS Pre-study	0.0887	0.6126	0.5435	-0.2036	0.3809
Less Activity than those of Similar Age	0.2226	2.5360	0.0151	0.0453	0.3998
More Activity than those of Similar Age	0.2094	2.1343	0.0388	0.0113	0.4074

c. Association between Number of INRs out of range during intervention period and Self-reported Physical Activity Level. i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.267
Adjusted R Square	0.195
Standard Error	6.840
F statistic	3.727
p-value	0.011

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	4.1094	1.6420	0.1082	-0.9448	9.1637
Less Activity than those of Similar Age	6.9341	2.7427	0.0090	1.8283	12.0400
More Activity than those of Similar Age	4.5412	1.6178	0.1134	-1.1277	10.2101
Vitamin K Group	-2.6540	-1.2771	0.2088	-6.8510	1.5429
# INRs out of Range Prestudy	0.5470	1.9348	0.0599	-0.0240	1.1179

d. Association between number of dose changes during intervention period and self-reported physical activity level i) Regression Statistics with F-Test for overall model

significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.212
Adjusted R Square	0.135
Standard Error	3.885
F statistic	2.757
p-value	0.0405

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	2.3662	1.6678	0.1030	-0.4990	5.2315
Less Activity than those of Similar Age	3.6281	2.5588	0.0143	0.7646	6.4917
More Activity than those of Similar Age	3.0372	1.9173	0.0622	-0.1619	6.2364
Vitamin K Group	-1.4367	-1.2172	0.2305	-3.8206	0.9471
# Dose Changes Prestudy	0.2131	1.4709	0.1490	-0.0795	0.5058

Table 4.6.8 Effect of possessing at least one medical comorbidity (Active Cancer, Diabetes, Hypertension, or Inflammatory Bowel Disease) on measures of anticoagulation control during study period

a. Association between Time in Therapeutic Range during the intervention period and the Presence of at least one Medical Comorbidity (Active Cancer, Diabetes, Hypertension, or Inflammatory Bowel Disease) i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.080
Adjusted R Square	0.014

Standard Error	0.170
F statistic	1.213
p-value	0.317

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	0.5029	5.252	0.000	0.30965	0.6961
Vitamin K Group	-0.0254	-0.4738	0.638	-0.1333	0.0826
% TTR pre study	0.2481	1.6207	0.113	-0.0608	0.5571
Presence of at Least One Medical Comorbidity	0.0573	1.0669	0.292	-0.0511	0.1656

b. Association between Standard Deviation of INRs during the intervention period and the Presence of at least one Medical Comorbidity (Active Cancer, Diabetes, Hypertension, or Inflammatory Bowel Disease) i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.215
Adjusted R Square	0.159
Standard Error	0.253
F statistic	3.833
p-value	0.016

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	0.6167	4.8067	0.0000	0.3578	0.8756
Vitamin K Group	-0.2005	-2.5166	0.0158	-0.3613	-0.0397
STDEV INRS Pre-study	0.1554	1.0341	0.3070	-0.1479	0.4588
Presence of at Least One Medical Comorbidity	-0.0791	-0.9885	0.3286	-0.2406	0.0824

c. Association between Number of INRs out of range during intervention period and the Presence of at least one Medical Comorbidity (Active Cancer, Diabetes, Hypertension, or Inflammatory Bowel Disease) i) Regression Statistics with F-Test for

overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.183
Adjusted R Square	0.125
Standard Error	7.132
F statistic	3.1409
p-value	0.035

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	7.6111	3.1562	0.0030	2.7446	12.4777
Presence of at Least One Medical Comorbidity	-3.6687	-1.6218	0.1123	-8.2337	0.8963
Vitamin K Group	-0.4411	-0.1966	0.8451	-4.9696	4.0873
# INRs out of Range Prestudy	0.7629	2.6434	0.0115	0.1805	1.3453

d. Association between Number of dose changes during intervention period and the Presence of at least one Medical Comorbidity (Active Cancer, Diabetes, Hypertension, or Inflammatory Bowel Disease) i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.098
Adjusted R Square	0.033
Standard Error	4.107
F statistic	1.5180
p-value	0.224

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	4.3236	3.2071	0.0026	1.6029	7.0442
Presence of at Least One Medical Comorbidity	-1.1764	-0.9006	0.3730	-3.8126	1.4598

Vitamin K Group	-0.4242	-0.3281	0.7445	-3.0336	2.1853
# Dose Changes Prestudy	0.2912	1.9121	0.0627	-0.0161	0.5986

Table 4.6.9 Effect of Total Number of Medications at Baseline and Total Number of Interacting Medications at Baseline on measures of anticoagulation control during study period

a. Association between Time in Therapeutic Range during intervention period and Total Number of Medications at Baseline and Total Number of Interacting Medications at Baseline i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.176
Adjusted R Square	0.096
Standard Error	0.163
F statistic	2.19
p-value	0.087

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	0.4660	5.0214	0.0000	0.2786	0.6535
Vitamin K Group	-0.0151	-0.3125	0.7562	-0.1126	0.0824
% TTR pre study	0.2437	1.6643	0.1037	-0.0520	0.5395
Total Number of Meds at Baseline	0.0114	1.3520	0.1838	-0.0057	0.0286
Total Number of Interacting Meds at Baseline	0.0486	1.1509	0.2564	-0.0367	0.1338

b. Association between Standard deviation of INRs during intervention period and Total Number of Medications at Baseline and Total Number of Interacting Medications at Baseline i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.211
Adjusted R Square	0.134
Standard Error	0.257
F statistic	2.737
p-value	0.042

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	0.6229	4.6732	0.0000	0.3537	0.8921
Vitamin K Group	-0.2230	-2.9305	0.0055	-0.3767	-0.0693
STDEV INRS Pre-study	0.1585	1.0385	0.3051	-0.1497	0.4666
Total Number of Meds at Baseline	-0.0099	-0.7401	0.4635	-0.0370	0.0171
Total Number of Interacting Meds at Baseline	-0.0013	-0.0196	0.9845	-0.1360	0.1334

c. Association between Number of INRs out of range during intervention period and Total Number of Medications at Baseline and Total Number of Interacting Medications at Baseline i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.163
Adjusted R Square	0.081
Standard Error	7.306
F statistic	1.998
p-value	0.113

iii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	8.2173	3.0258	0.0043	2.7328	13.7018
Vitamin K Group	-1.4884	-0.6879	0.4954	-5.8579	2.8812
# INRs out of Range Prestudy	0.7011	2.3600	0.0231	0.1012	1.3010
Total Number of Meds at Baseline	-0.2712	-0.7069	0.4836	-1.0458	0.5035
Total Number of Interacting Meds at Baseline	-1.0249	-0.5379	0.5936	-4.8732	2.8234

d. Association between Number of dose changes during intervention period and Total Number of Medications at Baseline and Total Number of Interacting Medications at Baseline i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.089
Adjusted R Square	0.000
Standard Error	4.178
F statistic	0.995
p-value	0.421

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	4.4683	3.0161	0.0044	1.4764	7.4602
Vitamin K Group	-0.7757	-0.6270	0.5341	-3.2742	1.7228
# Dose Changes Prestudy	0.2724	1.7705	0.0841	-0.0383	0.5831
Total Number of Meds at Baseline	-0.1165	-0.5357	0.5951	-0.5559	0.3228
Total Number of Interacting Meds at Baseline	0.0100	0.0093	0.9927	-2.1800	2.2001

Table 4.6.10 Effect of *2 polymorphisms in the CYP2C9 gene (*1*2, *2*2) on measures of anticoagulation control during study period

a. Association between Time in Therapeutic Range during intervention period and *2 polymorphisms in the CYP2C9 gene (*1*2, *2*2). i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.104
Adjusted R Square	0.040

Standard Error	0.168
F statistic	1.631
p-value	0.197

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	0.52272	5.6625	0.000	0.3364	0.70902
Vitamin K Group	-0.0082	-0.166	0.869	-0.1084	0.09191
% TTR pre study	0.20881	1.3726	0.177	-0.0982	0.51583
Presence of CYP2C9 *2 Polymorphism	0.09217	1.5243	0.135	-0.0299	0.2142

b. Association between Standard deviation of INRs during intervention period and *2 polymorphisms in the CYP2C9 gene (*1*2, *2*2). i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.205
Adjusted R Square	0.149
Standard Error	0.255
F statistic	3.6181
p-value	0.021

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	0.6063	4.7132	0.0000	0.3467	0.8659
Vitamin K Group	-0.2266	-3.0119	0.0044	-0.3784	-0.0748
STDEV INRS Pre-study	0.1558	1.0287	0.3095	-0.1498	0.4614
Presence of CYP2C9 *2 Polymorphism	-0.0619	-0.6775	0.5018	-0.2463	0.1225

c. Association between Number of INRs out of range during intervention period and *2 polymorphisms in the CYP2C9 gene (*1*2, *2*2). i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.171
Adjusted R Square	0.112
Standard Error	7.185
F statistic	2.8875
p-value	0.047

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	7.5895	3.1101	0.0034	2.6649	12.5142
Vitamin K Group	-1.6333	-0.7699	0.4457	-5.9145	2.6480
# INRs out of Range Pre-study	0.7172	2.4801	0.0172	0.1336	1.3008
Presence of CYP2C9 *2 Polymorphism	-3.6064	-1.4038	0.1677	-8.7910	1.5782

d. Association between Number of dose changes during intervention period and *2 polymorphisms in the CYP2C9 gene (*1*2, *2*2). i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.091
Adjusted R Square	0.026
Standard Error	4.123
F statistic	1.3989
p-value	0.256

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	4.2944	3.1591	0.0029	1.5511	7.0377
Vitamin K Group	-0.8099	-0.6653	0.5095	-3.2665	1.6467
# Dose Changes Prestudy	0.2764	1.8222	0.0755	-0.0297	0.5825
Presence of CYP2C9 *2 Polymorphism	-1.0244	-0.6946	0.4911	-4.0004	1.9516

Table 4.6.11 Effect of *3 polymorphisms in the CYP2C9 gene (*1*3, *3*3) on measures of anticoagulation control during study period

a. Association between Time in Therapeutic Range during intervention period and *3 polymorphisms in the CYP2C9 gene (*1*3, *3*3). Regression Statistics ii) F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.055
Adjusted R Square	-0.012
Standard Error	0.172
F statistic	0.8225
p-value	0.489

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	0.5223	5.461	0.000	0.3293	0.7153
Vitamin K Group	-0.0064	-0.125	0.901	-0.1094	0.0966
% TTR pre study	0.2461	1.543	0.130	-0.0757	0.5679
Presence of CYP2C9 *3 Polymorphism	-0.0189	-0.178	0.859	-0.2332	0.1953

b. Association between STDEV INRs during intervention period and *3 polymorphisms in the CYP2C9 gene (*1*3, *3*3). i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.219
Adjusted R Square	0.163
Standard Error	0.253
F statistic	3.9298

p-value	0.015

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	0.5917	4.7497	0.0000	0.3403	0.8431
Vitamin K Group	-0.2340	-3.1295	0.0032	-0.3849	-0.0831
STDEV INRS Pre-study	0.1764	1.1749	0.2467	-0.1266	0.4794
Presence of CYP2C9 *3 Polymorphism	-0.1669	-1.1000	0.2776	-0.4731	0.1393

c. Association between Number of INRs out of range during intervention period and *3 polymorphisms in the CYP2C9 gene (*1*3, *3*3). i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.133
Adjusted R Square	0.071
Standard Error	7.347
F statistic	2.151
p-value	0.108

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	7.0367	2.7485	0.0088	1.8701	12.2033
Vitamin K Group	-1.7387	-0.7994	0.4285	-6.1280	2.6505
# INRs out of Range Prestudy	0.6998	2.3152	0.0256	0.0898	1.3097
Presence of CYP2C9 *3 Polymorphism	-1.0230	-0.2274	0.8212	-10.0997	8.0537

d. Association between Number of dose changes during intervention period and *3 polymorphisms in the CYP2C9 gene (*1*3, *3*3). i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.080
Adjusted R Square	0.015
Standard Error	4.147
F statistic	1.224
p-value	0.313

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	4.0847	2.9222	0.0056	1.2638	6.9055
Vitamin K Group	-0.8258	-0.6727	0.5048	-3.3032	1.6516
# Dose Changes Pre-study	0.2748	1.7704	0.0839	-0.0384	0.5879
Presence of CYP2C9 *3 Polymorphism	0.0916	0.0362	0.9713	-5.0083	5.1914

Table 4.6.12 Effect of polymorphisms in VKORC1 -1639 G>A (GA, AA) on measures of anticoagulation control during study period

a. Association between Time in Therapeutic Range during intervention period and polymorphisms in VKORC1 -1639 G>A (GA, AA) i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.101
Adjusted R Square	0.036
Standard Error	0.168
F statistic	1.566
p-value	0.212

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	0.5747	5.8264	0.000	0.3757	0.77382
Vitamin K Group	-0.0056	-0.113	0.910	-0.1059	0.09467
% TTR pre study	0.1801	1.1512	0.256	-0.1356	0.49583

GA or AA	-0.099	-1.463	0.151	-0.2355	0.03756

b. Association between Standard deviation of INRs during intervention period and polymorphisms in VKORC1 -1639 G>A (GA, AA) i) Regression Statistics ii) F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.260
Adjusted R Square	0.207
Standard Error	0.246
F statistic	4.926
p-value	0.005

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	0.5541	4.5245	0.0000	0.3069	0.8012
Vitamin K Group	-0.2305	-3.1753	0.0028	-0.3769	-0.0840
STDEV INRs Pre-study	0.1677	1.1508	0.2563	-0.1264	0.4617
GA or AA	0.1818	1.9004	0.0643	-0.0113	0.3748

c. Association between Number of INRs out of range during intervention period and polymorphisms in VKORC1 -1639 G>A (GA, AA) i) Regression Statistics ii) F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.140
Adjusted R Square	0.078
Standard Error	7.320
F statistic	2.272
p-value	0.094

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	6.8367	2.8145	0.0074	1.9345	11.7388
Vitamin K Group	-1.7243	-0.7979	0.4294	-6.0853	2.6367
# INRs out of Range Prestudy	0.6720	2.2203	0.0319	0.0612	1.2828
GA or AA	1.7726	0.6059	0.5479	-4.1317	7.6770

d. Association between Number of dose changes during intervention period and polymorphisms in VKORC1 -1639 G>A (GA, AA) i) Regression Statistics ii) F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.095
Adjusted R Square	0.031
Standard Error	4.113
F statistic	1.4769
p-value	0.235

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	4.0544	3.0535	0.0039	1.3749	6.7340
Vitamin K Group	-0.8492	-0.6994	0.4881	-3.2994	1.6010
# Dose Changes Prestudy	0.2468	1.5958	0.1180	-0.0653	0.5589
GA or AA	1.3666	0.8353	0.4083	-1.9350	4.6682

Table 4.6.13 Effect of polymorphisms in CYP4F2 1347 C>T (CT, TT) on measures of anticoagulation control during the study period

a. Association between Time in Therapeutic Range during intervention period and polymorphisms in CYP4F2 1347 C>T (CT, TT) i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.055
Adjusted R Square	-0.013
Standard Error	0.172
F statistic	0.8132
p-value	0.494

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	0.526	5.4319	0.000	0.3306	0.7215
Vitamin K Group	-0.005	-0.1002	0.921	-0.1094	0.0991
% TTR pre study	0.2385	1.5363	0.132	-0.0748	0.5519
CT or TT mutation	-0.004	-0.0738	0.942	-0.1152	0.1071

b. Association between Standard deviation of INRs during intervention period and polymorphisms in CYP4F2 1347 C>T (CT, TT) i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes(H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.197
Adjusted R Square	0.139
Standard Error	0.256
F statistic	3.4286
p-value	0.025

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	0.5890	4.5123	0.0001	0.3256	0.8524
Vitamin K Group	-0.2271	-2.9601	0.0050	-0.3820	-0.0723
STDEV INRS Pre-study	0.1628	1.0661	0.2925	-0.1454	0.4709
CT or TT mutation	-0.0038	-0.0458	0.9637	-0.1697	0.1622

c. Association between Number of INRs out of range during intervention period and polymorphisms in CYP4F2 1347 C>T (CT, TT) i) Regression Statistics with F-Test for

overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.132
Adjusted R Square	0.070
Standard Error	7.351
F statistic	2.1331
p-value	0.110

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	6.8945	2.7802	0.0081	1.8899	11.8992
Vitamin K Group	-1.6716	-0.7593	0.4519	-6.1146	2.7714
# INRs out of Range Prestudy	0.7157	2.4127	0.0203	0.1171	1.3144
CT or TT mutation	-0.1873	-0.0796	0.9369	-4.9344	4.5597

d. Association between Number of dose changes during intervention period and polymorphisms in CYP4F2 1347 C>T (CT, TT) i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.084
Adjusted R Square	0.018
Standard Error	4.139
F statistic	1.2813
p-value	0.2932

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	4.0010	2.9465	0.0052	1.2607	6.7413
Vitamin K Group	-0.9129	-0.7364	0.4656	-3.4146	1.5888
CT or TT mutation	0.5267	0.3975	0.6930	-2.1477	3.2011
# Dose Changes Prestudy	0.2688	1.7601	0.0857	-0.0394	0.5770

Table 4.6.14 Effect of Baseline Adherence as measured by the BMQ Recall Screen and BMQ Regimen Screen on measures of anticoagulation control during the study period

a. Association between Time in Therapeutic Range during intervention period and Baseline Adherence as measured by the BMQ Recall Screen and BMQ Regimen Screen. i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.066
Adjusted R Square	-0.025
Standard Error	0.173
F statistic	0.7235
p-value	0.581

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	0.5208	5.370	0.000	0.32495	0.7166
Vitamin K Group	-0.0074	-0.1437	0.886	-0.1110	0.0963
% TTR pre study	0.2560	1.622	0.112	-0.0627	0.5746
BMQ Recall Screen	-0.0627	-0.6696	0.507	-0.2518	0.1264
BMQ Regimen Screen	0.00871	0.1293	0.898	-0.1277	0.1452

b. Association between Standard deviation of INRs during intervention period and Baseline Adherence as measured by the BMQ Recall Screen and BMQ Regimen Screen. i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.200
Adjusted R Square	0.122
Standard Error	0.259

F statistic	2.5614
p-value	0.053

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	0.6058	4.4159	0.0001	0.3287	0.8828
Vitamin K Group	-0.2293	-2.9974	0.0046	-0.3838	-0.0748
STDEV INRS Pre-study	0.1515	0.9617	0.3419	-0.1666	0.4695
BMQ Recall Screen	-0.0310	-0.2247	0.8233	-0.3100	0.2480
BMQ Regimen Screen	-0.0209	-0.2034	0.8398	-0.2287	0.1869

c. Association between Number of INRs out of range during intervention period and Baseline Adherence as measured by the BMQ Recall Screen and BMQ Regimen Screen. i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.138
Adjusted R Square	0.054
Standard Error	7.416
F statistic	1.640
p-value	0.183

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	6.6605	2.5880	0.0133	1.4630	11.8579
Vitamin K Group	-1.6533	-0.7542	0.4550	-6.0803	2.7738
# INRs out of Range Prestudy	0.7397	2.4460	0.0188	0.1290	1.3504
BMQ Recall Screen	2.0882	0.5208	0.6053	-6.0089	10.1852
BMQ Regimen Screen	-0.9169	-0.3162	0.7534	-6.7727	4.9389

d. Association between Number of dose changes during intervention period and Baseline Adherence as measured by the BMQ Recall Screen and BMQ Regimen Screen. i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.138
Adjusted R Square	0.054
Standard Error	7.416
F statistic	1.640
p-value	0.183

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	3.8215	2.6724	0.0108	0.9335	6.7095
Vitamin K Group	-0.7823	-0.6343	0.5294	-3.2732	1.7086
# Dose Changes Prestudy	0.2887	1.8631	0.0696	-0.0242	0.6017
BMQ Recall Screen	1.3794	0.6143	0.5424	-3.1551	5.9138
BMQ Regimen Screen	0.0132	0.0081	0.9936	-3.2656	3.2919

Table 4.6.15 Effect of Total Score on Anticoagulation Knowledge Assessment (%) on measures of anticoagulation control during study period

a. Association between Time in Therapeutic Range during intervention period and Total Score on Anticoagulation Knowledge Assessment (%) at Baseline. i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.062
Adjusted R Square	-0.005
Standard Error	0.172
F statistic	0.9189
p-value	0.440

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	0.4577	2.9805	0.005	0.1478	0.7676
Vitamin K Group	-0.0009	-0.0169	0.987	-0.1049	0.1032
% TTR pre study	0.2372	1.5358	0.132	-0.0745	0.5488
AKA Total Score	0.0974	0.5524	0.584	-0.2585	0.4533

b. Association between Standard deviation of INRs during intervention period and Total Score on Anticoagulation Knowledge Assessment (%) at Baseline. i) Regression Statistics with F-Test for overall model significance(H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes(H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.199
Adjusted R Square	0.142
Standard Error	0.256
F statistic	3.4886
p-value	0.024

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	0.5176	2.3333	0.0245	0.0699	0.9652
Vitamin K Group	-0.2226	-2.9028	0.0059	-0.3773	-0.0678
STDEV INRS Pre-study	0.1629	1.0752	0.2884	-0.1429	0.4688
AKA Total Score	0.1007	0.3831	0.7035	-0.4296	0.6310

c. Association between Number of INRs out of range during intervention period and Total Score on Anticoagulation Knowledge Assessment (%) at Baseline. i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.143
Adjusted R Square	0.082
Standard Error	7.303
F statistic	2.3435
p-value	0.0867

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	2.8795	0.4906	0.6263	-8.9651	14.7240
Vitamin K Group	-1.4160	-0.6467	0.5214	-5.8349	3.0029

# INRs out of Range Prestudy	0.7248	2.4626	0.0180	0.1308	1.3187
AKA Total Score	5.5926	0.7444	0.4608	-9.5682	20.7535

Regression Parameter	With Outlier[A]	Without Outlier	% Change
R Square[C]	0.1434	0.1514	5.59
Adjusted R Square	0.0822	0.0893	8.66
Standard Error	7.3035	7.3498	0.634
Intercept	2.879	2.7297	-5.201
Vitamin K Group	-1.416	-1.1970	-15.47
# INRs out of Range Prestudy[B]	0.7248	0.8327	14.89
AKA Tot Score	5.5926	4.803	-14.12

[A]Outlier (N= 1 outlier with AKA Score =0.25, Standardized Residuals of Predicted Y = -3.09).
[B]P-value of regression coefficient with outlier ($p<0.05$) and without outlier ($p<0.05$)
[C] F statistic and p-value of regression model with outlier ($F=2.34$, $p=0.0867$). F statistic and p-value of regression model without outlier ($F=2.4385$, $p=0.078$)

d. Association between Number of dose changes during intervention period and Total Score on Anticoagulation Knowledge Assessment (%) at Baseline. i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes(H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.089
Adjusted R Square	0.024
Standard Error	4.126
F statistic	1.3756
p-value	0.263

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	2.1630	0.6601	0.5128	-4.4494	8.7753
Vitamin K Group	-0.6889	-0.5569	0.5805	-3.1854	1.8076
# Dose Changes Pre-study	0.2765	1.8213	0.0757	-0.0299	0.5829
AKA Tot Score	2.7428	0.6468	0.5213	-5.8156	11.3012

Table 4.6.16 Effect of the Number of Missed INR Appointments during the study period on measures of anticoagulation control during study period

a. Association between Time in Therapeutic Range during intervention period and the Number of Missed INR Appointments during the study period i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes(H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.133
Adjusted R Square	0.068
Standard Error	0.169
F statistic	2.0384
p-value	0.124

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	0.5677	5.5248	0.0000	0.3601	0.7754
Vitamin K Group	0.0022	-0.0438	0.9653	-0.1060	0.1015
% TTR pre study	0.2050	1.2812	0.2075	-0.1184	0.5283
Number of INR appointments missed during Study	-0.0209	-1.8076	0.0782	-0.0443	0.0025

b. Association between Standard deviation of INRs during intervention period and the Number of Missed INR Appointments during the study period i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.278
Adjusted R Square	0.227
Standard Error	0.243
F statistic	5.4000
p-value	0.003

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	0.5835	4.8738	0.0000	0.3419	0.8251
Vitamin K Group	-0.2274	-3.1720	0.0028	-0.3720	-0.0827
STDEV INRS Pre-study	0.1068	0.7301	0.4694	-0.1883	0.4019
Number of INR appointments missed during Study	0.02687	2.1802	0.0349	0.0020	0.0517

c. Association between Number of INRs out of range during intervention period and the Number of Missed INR Appointments during the study period i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes(H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.145
Adjusted R Square	0.084
Standard Error	7.295
F statistic	2.3804
p-value	0.083

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	6.2683	2.4785	0.0173	1.1644	11.3723
DNA During Study	0.2942	0.8064	0.4246	-0.4420	1.0304
Vitamin K Group	-1.6956	-0.7874	0.4355	-6.0415	2.6502
# INRs out of Range Prestudy	0.7257	2.4685	0.0177	0.1324	1.3189

d. Association between Number of Dose changes during intervention period and the Number of Missed INR Appointments during the study period i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.105
Adjusted R Square	0.042
Standard Error	4.090
F statistic	1.6506
p-value	0.192

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	3.5174	2.4697	0.0177	0.6432	6.3915
Vitamin K Group	-0.8249	-0.6833	0.4982	-3.2610	1.6113
DNA During Study	0.2248	1.0848	0.2842	-0.1934	0.6429
# Dose Changes Pre-study	0.3015	1.9759	0.0548	-0.0064	0.6094

Table 4.6.17 Effect of the Presence of Self-reported warfarin/study medication dosing errors (includes missed doses or taking incorrect dose) during the study period on measures of anticoagulation control during study period

a. Association between Time in Therapeutic Range during intervention period and Presence of Self-reported warfarin/study medication dosing errors (includes missed doses and taking incorrect dose) during the intervention period i) Regression Statistics ii) F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.346
Adjusted R Square	0.300
Standard Error	0.143
F statistic	7.4210
p-value	0.000

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	0.6502	7.7389	0.0000	0.4806	0.8198
Vitamin K Group	-0.0151	-0.3554	0.7241	-0.1007	0.0705
% TTR pre study	0.1052	0.7943	0.4315	-0.1621	0.3726
Presence of Dosing Error	-0.2371	-4.3293	0.0001	-0.3477	-0.1266

b. Association between standard deviation of INRs during intervention period and Presence of Self-reported warfarin/study medication dosing errors (includes missed doses and taking incorrect dose) during the intervention period i) Regression Statistics ii) F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.385
Adjusted R Square	0.341
Standard Error	0.224
F statistic	8.7571
p-value	0.000

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	0.5360	4.8090	0.0000	0.3111	0.7609
Vitamin K Group	-0.2199	-3.3205	0.0019	-0.3535	-0.0862
STDEV INRS Pre-study	0.1493	1.1236	0.2676	-0.1189	0.4176
Presence of Dosing Error	0.2989	3.5838	0.0009	0.1306	0.4673

c. Association between number of INRs out of range during intervention period and Presence of Self-reported warfarin/study medication dosing errors (includes missed doses and taking incorrect dose) during the intervention period i) Regression Statistics ii) F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.492
Adjusted R Square	0.456
Standard Error	5.624
F statistic	13.5603
p-value	0.000

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	6.9031	3.6989	0.0006	3.1368	10.6694
Vitamin K Group	-1.3485	-0.8116	0.4216	-4.7014	2.0044
# INRs out of Range Prestudy	0.3237	1.3635	0.1800	-0.1554	0.8028
Presence of Dosing Error	11.9661	5.4552	0.0000	7.5394	16.3928

d. Association between number of dose changes during intervention period and Presence of Self-reported warfarin/study medication dosing errors (includes missed doses and taking incorrect dose) during the intervention period i) Regression Statistics ii) F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.391
Adjusted R Square	0.347
Standard Error	3.375
F statistic	8.9839
p-value	0.000

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	3.5098	3.2021	0.0026	1.2978	5.7218
Vitamin K Group	-0.6707	-0.6730	0.5047	-2.6822	1.3407
Presence of Dosing Error	5.8835	4.6269	0.0000	3.3173	8.4497
# Dose Changes Prestudy	0.1800	1.4316	0.1597	-0.0738	0.4338

Table 4.6.18 Effect of a Medication Change (addition or discontinuation of medication) during the study period on measures of anticoagulation control during study period

a. Association between Time in Therapeutic Range during intervention period and presence of a Medication Change (addition or discontinuation of medication) during the Intervention Period i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.055
Adjusted R Square	-0.012
Standard Error	0.172
F statistic	0.8201
p-value	0.490

iii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	0.5303	5.2312	0.0000	0.3257	0.7349
Vitamin K Group	-0.0073	-0.1415	0.8881	-0.1120	0.0973
% TTR pre study	0.2348	1.4918	0.1432	-0.0829	0.5525
Presence of Medication Change	-0.0095	-0.1584	0.8749	-0.1298	0.1109

b. Association between standard deviation of INRs during intervention period and presence of a Medication Change (addition or discontinuation of medication) during

the Intervention Period i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes(H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.207
Adjusted R Square	0.150
Standard Error	0.255
F statistic	3.6484
p-value	0.020

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	0.6025	4.7374	0.0000	0.3458	0.8591
Vitamin K Group	-0.2174	-2.8426	0.0069	-0.3717	-0.0631
STDEV INRS Pre-study	0.1131	0.6817	0.4992	-0.2218	0.4480
Medication Change	0.0696	0.7293	0.4699	-0.1230	0.2623

c. Association between number of INRs out of range during intervention period and presence of a Medication Change (addition or discontinuation of medication) during the Intervention Period i) Regression Statistics with F-Test for overall model significance(H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes (H_0: $\beta_i = 0$)

i)

Regression Statistics	*Value*
R Square	0.132
Adjusted R Square	0.070
Standard Error	7.351
F statistic	2.1327
p-value	0.110

ii)

	Coefficients	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	6.8347	2.7768	0.0082	1.8675	11.8020
Vitamin K Group	-1.6718	-0.7576	0.4529	-6.1253	2.7817
# INRs out of Range	0.7079	2.3043	0.0262	0.0879	1.3279

Prestudy					
Medication Change	0.1910	0.0734	0.9418	-5.0600	5.4421

d. Association between number of dose changes during intervention period and presence of a Medication Change (addition or discontinuation of medication) during the Intervention Period i) Regression Statistics with F-Test for overall model significance (H_0: $\beta_1 = \beta_2 = 0$) ii) Regression model; T tests of individual variable slopes(H_0: $\beta_i = 0$)

i)

Regression Statistics	***Value***
R Square	0.086
Adjusted R Square	0.021
Standard Error	4.133
F statistic	1.3256
p-value	0.279

ii)

	Coefficients	***t Stat***	***P-value***	***Lower 95%***	***Upper 95%***
Intercept	3.9867	2.9530	0.0051	1.2622	6.7113
Vitamin K Group	-0.7118	-0.5741	0.5690	-3.2139	1.7904
Medication Change	0.7715	0.5295	0.5993	-2.1693	3.7124
# Dose Changes Pre-study	0.2524	1.6054	0.1159	-0.0649	0.5697

4.7 Anticoagulation Knowledge Assessment [AKA] Results

Population responses to each of the questions in the Anticoagulation Knowledge Assessment [AKA] are presented in Table 4.7. The mean score was 67% (Range 24.14-89.66%] with no statistically significant difference between the Vitamin K and Placebo groups [p=0.8164]. Analysis of responses indicated that the most frequent correctly answered question was #11 (100% replying "b"), the most frequently incorrectly answered question was #7 (only 4% answering "d"), and the most frequently unanswered question was #21 (with 48% of respondents selecting no response). Evaluation of potential confounding effect of age and gender on total AKA score revealed no statistically significant association [Table 4.7.2]. Examination of scatterplots showed no evidence of correlation between AKA score and measures of anticoagulation control during the intervention period.

Table 4.7.1 Summary of responses provided on the Anticoagulation Knowledge Assessment [AKA] with proportion of responses selected by subjects [N=50].

Question Number	% Patients providing Correct Answer	% Patients providing Incorrect Answer	% Patients providing No Response
1	84	8	8
2	72	16	12
3	96	0	4
4	70	26	4
5	42	44	14
6	46	24	30
7	4	90	6
8	60	40	0
9	90	10	0
10	74	26	0
11	100	0	0

12	91	0	9
13	56	20	24
14	80	20	0
15	62	26	12
16	38	24	38
17	86	12	2
18	66	32	2
19	76	20	4
20	96	4	0
21	36	16	48
22	92	4	4
23	70	14	16
24	88	8	4
25	22	74	4
26	36	55	9
27	64	36	0
28	64	36	0
29	91	0	9

Table 4.7.2 Evaluation of the Relationship between Age and Gender and Total Score on the Anticoagulation Knowledge Assessment [AKA]

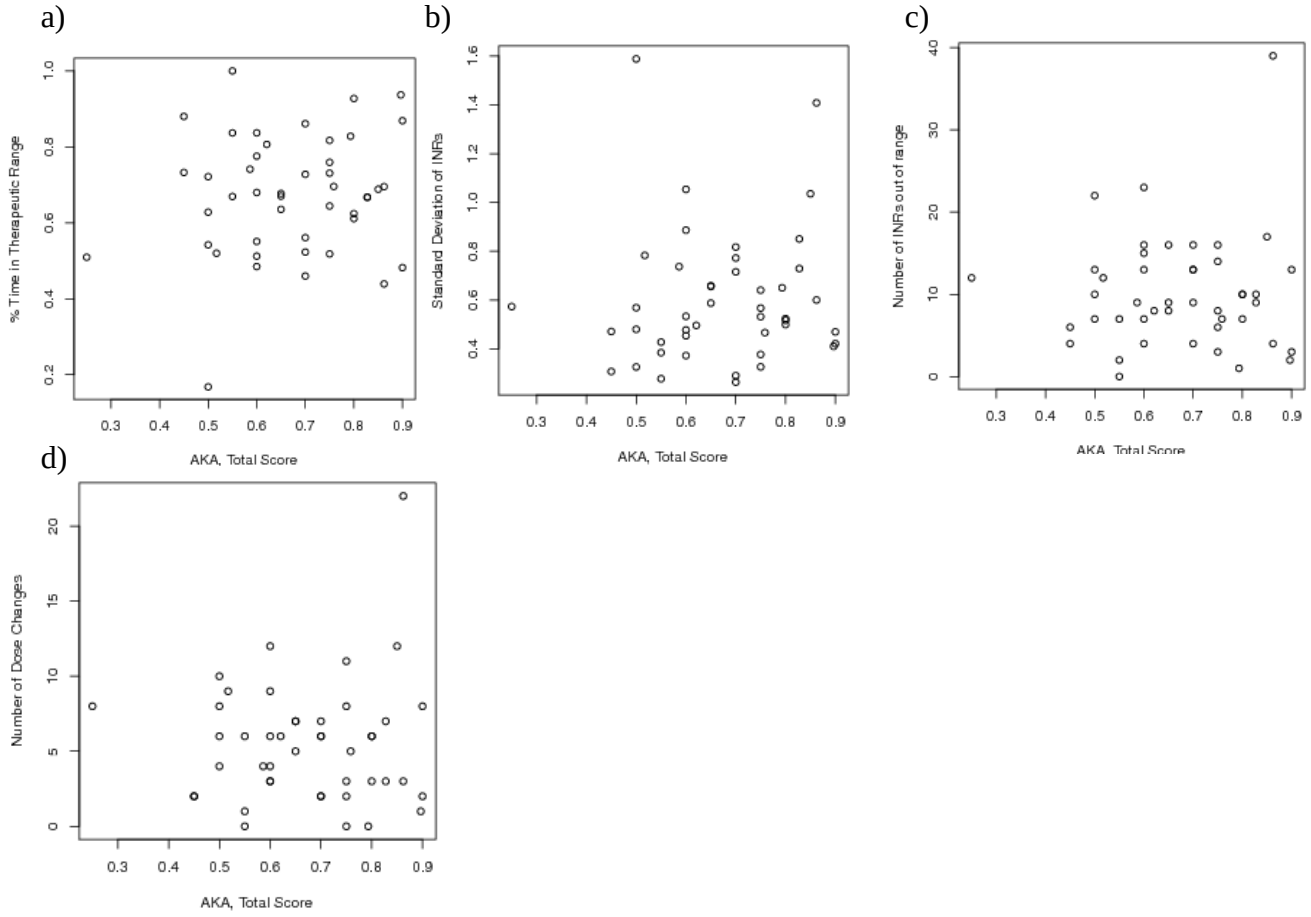
i)

Regression Statistics	***Value***
R Square	0.060
Adjusted R Square	0.017
Standard Error	0.146
F statistic	1.382
p-value	0.262

ii)

	Coefficients	***t Stat***	***P-value***	***Lower 95%***	***Upper 95%***
Intercept	0.7958	7.8664	0.0000	0.5918	0.9998
Age (at Enrolment)	-0.0023	-1.4494	0.1545	-0.0055	0.0009
Female Gender	0.0244	0.5566	0.5807	-0.0639	0.1126

Figure 3: Scatter plot of the relationship between Total Score on Anticoagulation Knowledge Assessment, AKA [Independent variable] and : a) % Time in Therapeutic range during the intervention period, % b) Standard deviation of INRs during the intervention period c) Number of INRs out of range during the intervention period d) Number of dose changes during the intervention period [N=50 patients]



4.8 BMQ Results

Evaluation of subject responses to the BMQ recall screen identified 5 subjects who self-reported missing at least one dose in the week preceding enrolment into the study [n=4 subjects missed 1 dose in the preceding week, n=1 subject missed 2 doses].

Evaluation of subject responses to BMQ regimen screen to identify potentially barriers to adherence showed the following. Five subjects (3 subjects Intervention arm, 2 subjects Placebo arm) responded that it was "somewhat hard" opening/closing the medication package. Ten subjects (5 subjects Intervention arm, 5 subjects Placebo arm) responded that it was "somewhat hard" remembering to take all of their medications. Two subjects (both in Placebo arm) responded that it was "somewhat hard" taking multiple pills at the same time.

Evaluation of responses to the belief screen [See Table 4.8.1] are summarized below and point to the fact that most subjects felt that warfarin was bothersome in some way [N=42/50]

Table 4.8.1: Responses from BMQ (Belief Screen) about Drug Efficacy and Bothersome Side Effects for patients followed in study [N=50]

Question	Response Option	Responses, n (%)
1) How well does WARFARIN work for you?	Well	13 (26)
	Okay	29 (58)
	Not Well	8 (16)
2) Does the WARFARIN Bother you in Any Way?	Yes	42 (84)
	No	8 (16)
If YES, how much it bothers you [N=42]	A lot	14 (34)
	Some	23 (55)
	A little	5 (12)
In what way does it bother you?	Going for INR testing	22 (52)
	Taking Medication daily	8 (19)
	Changing Doses frequently	5 (12)
	Controlling Diet	4 (10)
	Other[1]	3 (7)

[1]Communicating frequently with INR clinic (n=2), Disturbs ability to plan activities (n=1)

4.9 K-card Results

Response to the K-card dietary questionnaire was suboptimal in this study. 30 % of patients completed a Baseline K-card, 12% completed a Month 2 K-card, 14% completed a Month 4 K-card, and 12% completed a Month 6 K-card. The proportion of patients in this study who completed a baseline K-card, Month 2 K-card, Month 4 K-card, and Month 6 K-card was 12% [n=6].

On follow-up principal reasons for lack of completion among patients who did not complete any K-cards [Number of respondents, n=34] included: unable to quantify intake in measures reported on K-card (71%), feeling that current dietary variability was not captured on the K-card (59%), forgetting to chart food intake daily during the allocated time interval of the K-card (44%), and not eating any of the foods listed on the K-card (35%). Among patients who completed at least one K-card [Number of respondents, n= 12] principal reasons for lack of completion of additional K-card included: difficulty quantifying intake in measures reported on K-card (67%), inconvenience of having the K-card with them when having meals (75%), forgetting to chart food intake daily during the allocated time interval of the K-card (50%), having numerous days where no food listed on the K-card was consumed (25%).

Given the low response rate it was viewed that analysis of the relationship between Vitamin K intake measures obtained from the K-card and anticoagulation control would be spurious and hence was not done.

4.10 Medication Results

For the 50 patients enrolled and followed in this study a total of 162 medications (including Vitamins and Herbal Products; 134 medications if excluding Vitamins and Herbal

Products) were recorded at the baseline visit. From amongst the medications reported, 23 medication were deemed to be interacting according to the review article by Holbrook et al[64] (16 potentiating warfarin action, 7 inhibiting warfarin action). Among subjects enrolled and followed in the study, only one medication started at baseline was discontinued (n=1, Imuran). During the course of the study, n=11 subjects (7 placebo, 4 intervention) had a medication added. Medications added during the study period included: Modafinil, Keflex, Tylenol, Amoxicillin, Synthroid, Avodart, Amitriptaline, Cefazolin, Clonazepam, Macrobid, and Cipralex.

4.11 Interruption of Coumadin during Study Period

During the six month follow-up during the intervention period of the study, n=5 subjects had procedures that required them to interrupt/suspend their anticoagulation (n=4 intervention arm, n=1 placebo arm). The procedures performed and number of days that warfarin was held include: Laparoscopic vaginal hysterectomy (7 days), Cystoscopy guided biopsy (6 days), Gastric biopsy (5 days), Aspiration of shoulder (4 days), and Endoscopy for recurrent diarrhea (8 days). No statistically significant association was observed between having had a procedure during the study period that required coumadin interruption and measures of anticoagulation control (data not shown). Patients who were required to interrupt their warfarin therapy were also told to hold their intervention medication as well.

4.12 Reported Adverse Events

During the course of the study, no major bleeds [defined according to ISTH criteria: i) symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, or pericardial, or intramuscular with compartment

syndrome, and/or ii) Bleeding causing a fall in haemoglobin level of 20 g/L or more, or leading to transfusion of two or more units of whole blood or red cells] or venous thromboemboli were reported.

One episode of neuralgic pain was reported within 2 days of taking the study medication in a patient randomized to the placebo group. This patient had an underlying history of chronic pain and osteoarthritis. This patient electively withdrew from the study at day 8. A follow-up phone call in 1 week post withdrawal from study revealed that the pain was still present but to a lesser degree and was attributed to being due to the patient's underlying comorbidities. Two patients randomized to the Vitamin K group and 1 patient randomized to the placebo group reported episodes of diarrhoea upon initiation of study medication lasting 3, 2, and 4 days respectively. Two of the patients had a history of Crohn's disease and 1 patient had viral prodrome symptoms around the time of onset. All three of the aforementioned patients had resolution of their symptoms to baseline levels prior to study entry at the Month 2 follow-up and all three remained in the study to completion.

4.13 Rationale for Early Termination of Study

As stated in our sample size justification we had aimed to recruit 46 patients per arm for this clinical trial to ensure that it would be powered to detect a MCID of 10% (absolute difference) in the change score for percent time in therapeutic range. The rationale for concluding prior to achieving this result was two fold. First, examination of the CONSORT diagram of eligible patients revealed that from the initial 192 deemed eligible, only 46 had not yet been contacted for possible enrolment. Given that the overall enrolment as a function of solicitation was approximately 37% (54/146). It was deemed that we would need to recruit all of these patients as well as solicit all the patients for whom instability was in the

first two months of the preceding six months. Second, due to clinical responsibilities of the primary investigator (Habeeb Majeed), enrolment and follow-up became increasingly difficult. Hence after discussion with the GSC and Dr. Doug Coyle, it was deemed acceptable that the data collected so far would be sufficient for the purpose of a Masters' thesis.

5. DISCUSSION

In evaluating intervention effectiveness, our study did not demonstrate improvement in our primary outcome measure (change score of % TTR). However, this study did demonstrate a statistically significant improvement in anticoagulation control between the intervention and control group (p=0.0261), as measured by the change score of standard deviation of INRs (between the 6 month pre-intervention period and 6 month intervention period). Multivariate linear regression analysis of the standard deviation of INRs during the study period as a function of treatment allocation and pre-intervention INR standard deviation confirmed that allocation to the Vitamin K1 group was predictive of decreased INR standard deviation [Beta Vitamin K = -0.23, 95% C.I -0.38 to -0.08]. Change score and multivariate regression analysis showed no statistically significant association between other measures of anticoagulation control (i.e. number of INRs out of range or number of dose changes) and allocation to the Vitamin K arm. The aforementioned results are in concordance to results obtained in previous RCTs published prior to the initiation of this study. In comparing our results with those achieved by Sconce et al[23] (i.e: 28% absolute difference between the standard deviation of INRs in the Vitamin K and Placebo arms); we observed a 35% reduction in the standard deviation of INRs in the Vitamin K group relative to 4% in the control group (Absolute difference = 31%). In examining the similarities and

difference between the two studies we observed that our patient population, like that of the Sconce study, was predominantly Caucasian and derived from a specialized anticoagulation clinic. Both of the aforementioned factors, as stated in the introduction of this thesis, have been associated with improved anticoagulation control in the literature. The patient populations differed slightly with respect to age; with our patient population having a median age of 55 for the Vitamin K group (Sconce study Median age = 74.5 in the Vitamin K group) and 58 for the Placebo group (Sconce study Median age = 74.3 in the Placebo group). As stated in the introduction to this thesis, the literature [14, 36, 37, 86, 87] is split with younger age being more frequently associated with improved anticoagulation control. The two study populations also differed with respect to the primary indication for anticoagulation – our population being predominately venous thromboembolism and the Sconce study[23] enrolling exclusively atrial fibrillation patients.

Two randomized controlled trials were published after the initiation of this study and produced conclusions similar to this thesis with respect to intervention effectiveness. Dalloul et al[28] in a randomized controlled trial of 30 patients observed no statistically significant difference in the mean number of dose adjustments after treatment. The results of our study showed no statistically significant impact on number of dose changes during the intervention period for patients randomized to the Vitamin K group relative to placebo [95% C.I of Beta coefficient for Vitamin K = -2.24 to 1.41]. A second randomized controlled trial and dose finding study by Gebius et al[100] found that for patients randomized to receive 200 μg/day of Vitamin K, there was a non-significant improvement in percent time in therapeutic range relative to placebo 1.8% (95% CI:-3.6%-7.1%). The authors also noted that there was little incremental difference when patients were randomized to 100 μg/day, 150 μg/day, or 200 μg/day of Vitamin K1. It should be noted that both the Gebius et al[100] and Rombouts et

al[24] studies despite containing the largest number of patients randomized of any prior study – 400 and 200 respectively; utilized shorter half life anticoagulants (i.e. phenprocoumon, acenocoumoral) that have been shown to be associated with more unstable anticoagulation control[27, 65]. In addition, it should be noted that both Gebius et al[100] and Rombouts et al[24] enrolled all anticoagulated patients rather than targeting the intervention towards unstably anticoagulated patients.

Several conclusions were drawn from the multivariate analysis evaluating the impact of covariates such as clinical/demographic variables, anticoagulation related knowledge, medication usage, and genetic polymorphism in Vitamin K/warfarin metabolism genes. In examining the impact on anticoagulation control of age, gender, indication for anticoagulation, presence of medical co-morbidities (active cancer, hypertension, diabetes, IBD), total number of medications, BMI, presence of CYP2C9*2 polymorphism, presence of CYP2C9*3 polymorphism, presence of CYP4F2 C>T polymorphism, poor adherence according to the BMQ, Total Score on AKA, and presence of medication changes during the study period [see Table 4.6.1, Table 4.6.2, Table 4.6.3, Table 4.6.5, Table 4.6.8, Table 4.6.9, Table 4.6.10, Table.4.6.11, Table 4.6.13, Table 4.6.14, Table 4.6.15, Table 4.6.18], no statistically significant associations were observed. In the linear regression models that evaluated the impact of clinical covariates on the association between INR standard deviation as a function of treatment allocation – it was observed that treatment allocation to the Vitamin K group was consistently a predictive for decreased INR standard deviation.

When examining the impact of alcohol consumption [see Table 4.6.4] on intervention effectiveness and anticoagulation control, a potential association was seen. After adjusting for treatment allocation and pre-intervention anticoagulation control measures, consumption of $\geq$ 5 alcoholic drinks per week was associated with increasing standard deviation of INRs

relative to no alcohol consumption [95% CI of beta coefficient = 0.04 to 0.41]. The number of alcoholic drinks per week was also independently associated with increasing number of dose changes relative to non-drinkers during the intervention period [95% C.I of Beta coefficient for 1-4 drinks per week = 0.05 to 4.98; 95% C.I of Beta coefficient for $\geq$ 5 drinks per week = 2.39 to 7.99]. The consumption of $\geq$ 5 drinks per week was also associated with increasing number of INRs out of range relative to non-drinkers [95% C.I of Beta coefficient for $\geq$ 5 drinks per week = 1.61 to 12.32]. The implications of this finding would be that when considering the use of Vitamin K1 supplementation in an unstable patient, clinicians may get even more benefit by first encouraging their patient to limit alcohol usage if they are known to be a heavy consumer. The large confidence intervals around the aforementioned point estimates for the Beta coefficients is reflective of a small sample size and further study of this issue may be warranted.

When evaluating the impact of smoking [See Table 4.6.6] after adjusting for pre-intervention measures of anticoagulation control and treatment allocation; a non-statistically significant inverse association was observed with anticoagulation control during the intervention period. Smokers, relative to non-smokers, had a trend toward increasing standard deviation of INRs [Beta = 0.18, p=0.08], increasing number of INRs out of range [Beta = 5.05, p=0.07], and increasing dose changes [Beta = 2.79, p=0.08].

When evaluating the impact of patient self-reported physical activity on anticoagulation control during the intervention period [See Table 4.6.7] after adjusting for pre-intervention measures of anticoagulation control and treatment allocation, a statistically significant trend was observed. Patients who self-reported being Less Physically Active compared to others their age showed increased tendency for decreased percent time in therapeutic range [95% C.I of Beta coefficient = -0.26 to -0.02], increased INR standard

deviation [95% C.I of Beta coefficient = 0.05 to 0.40], increasing number of INRs out of range [95% C.I of Beta coefficient = 1.8 to 12], and increased number of dose changes [95% C.I of Beta coefficient = 0.76 to 6.49]. It should be noted that for patients who self-reported being More Physically Active compared to others their age also showed increased tendency for increased INR standard deviations [95% C.I of Beta coefficient = 0.01 to 0.41]. Given the subjective nature of the rating scale, these results should be interpreted with caution and the potential of other confounding variables may account for this association [i.e. patients who are less physically active may have a 'poorer' diet which in turn contributes to inadequate or highly variable Vitamin K levels]. Furthermore, despite the statistical significance in our models, the lack of a biologically plausible explanation that would account for increasing anticoagulation instability for both those who self-reported more and less physical activity (relative to their peers of similar age) led the authors to be cautious in stating it to be a predictor of anticoagulation instability.

When evaluating the impact of VKORC1 G>A polymorphisms [see Table 4.6.12] on measures of anticoagulation control during the intervention period after adjusting for pre-intervention measures of anticoagulation control and treatment allocation -- a positive trend towards significance was observed with INR standard deviation [Beta coefficient = 0.18, p=0.06]. Previous studies[102, 103] including a post-hoc analysis[103] of the trial done by Sconce and colleagues[23], demonstrated that the -1639 VKORC1 G>A exonic polymorphism is associated with decreased warfarin dose requirements. Sconce and colleagues[103] found in their analysis that the mean warfarin dose increase required after Vitamin K supplementation for the GG, GA, and AA genotypes to be 0.82 mg/day, 0.34 mg/day, and 0.00 mg/day respectively (i.e: individuals who possessed the polymorphism required less of a dose increase relative to wildtype). The resulting lower anticoagulation control among

homozygotes and heterozygotes individuals relative to wildtype may be due to the fact that warfarin dose adjustments are producing more variability in the warfarin sensitive individuals, thereby increasing time out of range. The resulting treatment implications would be that when supplementing with low dose Vitamin K1 in patients with these polymorphisms a slower and more cautious approach to warfarin dose adjustment would be advisable.

With respect to polymorphisms in CYP2C9, our results [see Table 4.6.10 and Table 4.6.11] differ slightly from the prior literature stated in the introduction to this manuscript. While we observed no statistically significant association between the presence of *2 or *3 polymorphisms and anticoagulation control, Tassies et al[61] in a retrospective cohort of 325 acenocoumoral anticoagulated patients noted that carriers of CYP2C9*3 spent less time within the therapeutic range [64.7±23.1%] than did patients with the CYP2C9*1/*1 genotype [75.1±22.0%, $p<0.01$]. The rationale for this discrepancy is likely due to the small sample size in our study with the number of *1*3 and *3*3 subjects in the study being 4 and 2 respectively. Additionally, with respect to polymorphisms in CYP4F2, to our knowledge at the time of initiation this is the first study to look at its influence in the context of Vitamin K1 supplementation. Multivariate linear regression analysis failed to elicit a statistically significant relationship between measures of anticoagulation control during the intervention period and presence of a CYP4F2 polymorphism (adjusting for pre-intervention measures of anticoagulation control and treatment allocation).

With regards to the lack of an association between the number of interacting medications/total medications and measures anticoagulation control, the rationale for this may be due to the fact that a medication (regardless of whether it is an interacting medication or not) if taken consistently can produce a predictable effect on anticoagulation parameters.

The impact of these medications on anticoagulation parameters can thus be compensated for by increasing or decreasing the dose of warfarin depending if the medication is one that inhibits or potentiates warfarin respectively, the net result being a negligible impact on anticoagulation control.

When evaluating the impact of missing INR appointments and dosing errors (i.e taking the incorrect dose or missing a dose) both were found to be independently associated with poor anticoagulation control [See Table 4.6.16, 4.6.17]. The presence of a dosing error during the 6 month intervention period was found to independently associated with increasing instability in measures of anticoagulation control during the intervention period. Positive associations were observed for standard deviation of INRs [95% C.I. of Beta = 0.13 to 0.47], number of dose changes [95% C.I. of Beta = 3.32 to 8.45], and number of INRs out of range [95% C.I. of Beta = 7.54 to 16.39]. An inverse association between the presence of a dosing error and % TTR during the intervention period was also observed [95% C.I. of Beta = -0.35 to -0.13]. Missed INR appointments were found to be independently associated with increasing INR standard deviation [95% C.I. of Beta = 0.002 to 0.05] and increasing number of INRs out of range [95% C.I. of Beta = 0.13 to 1.32]. It should be noted that there were trends towards significance of a relationship between missed INR appointments and % TTR (p-value of Beta coefficient = 0.08) and number of dose changes (p-value of Beta coefficient = 0.06). These results parallel with previous studies cited in the introduction of this thesis that demonstrated that as adherence decreases so too does anticoagulation control[42-45]. It should be noted that the results in this study relied on self-reporting of adherence and that there exists the potential for under-reporting. The rationale for choosing self-reporting as opposed to other methods (i.e: pill counting, electronic pill bottle opening) were two-fold. First, it was done to minimize the number of visits that the patient would

have to make to our clinic and thereby increase subject buy-in. Second, the use of self-reporting is very much reflective of how medication adherence is assessed in real world clinical practice. Both of the aforementioned reasons are in keeping with the pragmatic nature of this trial which was designed to assess intervention effectiveness in real world clinical practice.

In evaluating patient level responses to the Brief Medication Questionnaire (BMQ), no statistically significant associations were observed with measures of anticoagulation control during the intervention period as per multivariate regression. It should be noted that the number of patients who self-reported missing a dose in the week preceding study entry was small (n=5). Similarly the number of patients who self-reported potential barriers to adherence: difficulty "opening/closing the medication package, difficulty "remembering to take all pills", and difficulty "taking multiple pills at the same time" was also small (n= 5, 10, and 2 respectively) leading to cautious interpretation of conclusions. It should also be noted that previous studies[45] have shown that entry to a clinical trial can increase compliance on the part of unstable patients thereby leading to increased measures of anticoagulation control. Hence the use of the BMQ in previous studies as a screening tool to predict future non-compliance may not be methodologically appropriate. When evaluating results of the belief screen component of the BMQ, we see that most patients enrolled in this study do feel that warfarin works "well" or "okay" for them (84%). However, a significant of proportion of patients find it to be bothersome (84%) with attending INR testing being the most common reason reported (52%). These results potentially suggest that for patients who fail to achieve stable anticoagulation control while on Vitamin K antagonists, a trial of newer generation oral anticoagulants (e.g. Pradax™, Xarelto™) may be beneficial since they do not require INR monitoring. Potentially such a medication change could lead to increased

patient quality of life and improved therapeutic outcomes. Further research into the use of new oral anticoagulants in patients who failed to achieve stable anticoagulation control with Vitamin K antagonists may be of benefit.

With respect to our previously mentioned findings that anticoagulation knowledge (as measured by the AKA) is not independently associated with measures of anticoagulation control, these results parallel those reported in a study published after the initiation of this trial. Baker et al[101] in a retrospective cohort of n=185 patients also demonstrated no correlation between the patient's AKA score and INR control, defined as the count of the 10 previous INR values within goal range (Spearman rho = –0.022, P = 0.776). The authors also noted no significant associations between AKA score and TTR (Spearman rho = 0.015, P = 0.848) as well as Standard deviation of INRs (Spearman rho = 0.047, P = 0.550). The implications of a potentially positive association would have been that interventions aimed at increasing patient education could have been seen as an alternative avenue to explore to increase anticoagulation control in patients with significant variability prior to attempting Vitamin K. The aforementioned results are; however, in contrast to results by Tang and colleagues[47] who found that knowledge was related to age [r = -0.43, p<0.001] and noted a positive correlation between a patient's warfarin knowledge and the number of INR values that were within target range in the most recent 4 clinic visits [r = 0.20; p=0.024]. Furthermore, it should be noted that the questionnaire used by Tang and colleagues[47] was not psychometrically validated.

While it does not impact the conclusions made by the aforementioned studies, the data collection methods utilized in this study for the AKA may be superior to those of Baker and colleagues[101] due to the fact that the authors mention in their paper that the method of collection of survey data was not standardized. Patients in the Baker study[101] had the

opportunity to either complete the knowledge test in the clinic, take it home and return it by mail, or return it at their next scheduled appointment. A majority of patients in fact (n= 171 patients, 92.4%) completed the questionnaire outside of the facility. While subjects were expected to complete the questionnaire independently, the authors noted that there was no way to independently verify this. In our study the administration of the questionnaire was exclusively done at the Ottawa Hospital Thrombosis Clinic at the baseline visit with the research assistant present. The research assistant was instructed not to help the patient and the patients were instructed not to guess and should they not know the answer to a question to leave it blank.

The principle strength of this study was the fact for warfarin anticoagulated patients (for predominately venous thromboembolism) our study is the only one to use a commercially available preparation of Vitamin K1. Previous trials by Sconce et al[23] used an investigator developed liquid Vitamin K1 formulation that is unlikely to be readily adopted in clinical practice. Additionally, the trial by Rombouts et al[24] utilized shorter half life anticoagulants that have been shown to be associated with more unstable anticoagulation control[27, 65]. Furthermore, by having a study setting that was a specialized anticoagulation clinic ensured study that our patients received the highest possible quality of anticoagulation management; thereby, minimizing treatment center related impact on poor anticoagulation control.

Limitations of the study are the fact that the impact of dietary Vitamin K intake could not be assessed due to the low response rate to the K-card questionnaire. Additionally, a limitation of the study was the deviation from the initial definition of unstable control wherein patients who had their instability exclusively in the first two months of the preceding 6 months (i.e. in the preceding four months had no INRs out of range or dose

changes) were excluded from recruitment. Prior studies[24, 100] have shown that inclusion of all anticoagulated subjects (i.e. including already stable patients) did not result in improvement in anticoagulation control suggesting the intervention produces the most benefit in those who fail to achieve stable INR control. Future research could determine at what "cut-point" of INR stability vitamin K supplementation would cease to produce a statistically significant improvement in anticoagulation control. With regards to the inability to evaluate the impact of Vitamin K dietary variability on anticoagulation control in the intervention period due to low response rate; we do not feel that it will impact the underlying findings of this trial. Schurgers and colleagues[78] confirmed that a dose of at least 150 microgram or more per day of Vitamin K would be sufficient to override dietary variability. Furthermore, the lack of measurement of dietary Vitamin K intake is consistent with previous trials of this intervention[20, 24, 79, 100]. The rationale for using K-card as opposed to food diaries was two fold; first we felt it important to use a validated instrument in the assessment of dietary Vitamin K intake and felt that given that many foods do not contain appreciable amounts of Vitamin K it would be of limited utility to use diaries. Of note is that the K-card utilized in this trial was a modified version that included all foods listed in the original K-card as well as foods that had at least 25 micrograms per serving on USDA National Nutrient Database for Standard Reference, Release 18[104]. The rationale for doing this was that the original K-card was developed in a population that primarily ate an "American" diet and it was felt that foods that were not included but could have a potential for being consumed in a ethnically diverse Canadian population should be included (i.e.. Bok Choy).

An important point to note is that while our study and several aforementioned studies did show statistically significant changes in measures of anticoagulation control with

Vitamin K supplementation these may not translate into clinically relevant outcomes. Although van Walraven et al[11] determined in a Monte Carlo simulation study that a change in % TTR of 8.4% [Range 1.8-18%] would be associated with a decrease in hemorrhagic and thrombotic events -- neither our study, nor any previous study, has demonstrated a treatment effect of this magnitude. Supplementation with Vitamin K1 thus may not produce an appreciable change in bleeding or recurrent thrombotic events.

Therefore, our recommendations for clinicians who are considering vitamin K supplementation in patients who have unstable anticoagulation control are as follows: 1) Vitamin K can be expected to improve measures of anticoagulation control – namely standard deviation of INRs; 2) Vitamin K is unlikely to be effective as a population based intervention to improve anticoagulation control for all patients on Vitamin K antagonists and it should thus be targeted towards patients who have a history of unstable anticoagulation control. 3) If a clinician has the ability to perform genotypic analyses, one should be cautious of patients with a VKORC1 -1639 G>A polymorphism as the presence of at least one allele (which increases warfarin sensitivity) can increase risk of greater instability. Patients who have the aforementioned allelic variants and are being trialed on Vitamin K1 should have a more gradual and slower change to their warfarin dose. 4) Clinicians should ensure that other potential factors that can influence anticoagulation control are optimized; mainly recommending limiting alcoholic consumption (i.e. limiting drinks to $\leq$ 5 per week) and ensuring measures are in place to minimize missed INR appointments (i.e. telephone reminders) and dosing errors (i.e. clinical teaching).

The authors wish to note that while we are beginning an era with new oral anticoagulants that do not require monitoring supplanting Vitamin K antagonists as the preferred method of anticoagulation, there may continue to be a role for Vitamin K

supplementation. In an animal study on the now defunct direct thrombin inhibitor, Ximelgatran, Kamali et al[105] aimed to quantify the impact that a Vitamin K deficient diet versus a "normal" diet would have on the anticoagulant response of both Ximelgatran and warfarin. The authors observed that the anticoagulant activity of both ximelagatran and warfarin were significantly greater in rats on a Vitamin K deficient diet (6.1- and 12.3-times for PT, 2.6- and 5.1-times for APTT and 2.9- and 1.6-fold for ECT, respectively) compared to those on normal diet. Factor II activity was reduced by both ximelagatran (58%) and warfarin (44%) in rats on normal diet. However, factor II activity was virtually abolished (<0.1%) by both drugs in rats on vitamin K deficient diet. Based on the aforementioned results, ensuring that patients get an adequate and consistent intake of Vitamin K may be beneficial in improving anticoagulation response for patients on the new direct thrombin inhibitors (e.g. Dabigatran) and further research into this area may be warranted.

In conclusion, the results of this study are largely consistent with previous studies evaluating the impact of Vitamin K1 supplementation on anticoagulation control in unstable patients. Regression modelling and change score analysis demonstrated that Vitamin K1 supplementation reduces the standard deviation of INRs during the intervention period. In evaluating the potential for confounders and other variables that may independently predict anticoagulation stability it was found that a patient specific variable (i.e. $\geq$5 alcoholic drinks per week) and treatment specific variables (i.e. dosing errors, missed INR appointments) were independent predictors of poor anticoagulation control after adjusting for treatment group allocation and pre-intervention anticoagulation control measures. With regards to the impact of genetic polymorphisms in genes known to impact Vitamin K and warfarin metabolism, a trend towards significance was observed between increased standard deviation of INRs and GA or AA allelic variants at -1639 in the VKORC1 gene. An additional trend

was noticed with respect to Smoking and increased standard deviation of INRs, increased dose changes, and increased number of INRs out of range; however, this trend failed to reach statistical significance.

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APPENDIX

1. Anticoagulation Knowledge Assessment

(Correct Answers marked by * were not present on patient copies)

Patient ID _____

Data Collection Date: _____

1. Which one of these medications is recommended if you are taking Coumadin (warfarin) and want relief from a headache?
a. Advil
b. Motrin
c. Aspirin
d. Tylenol*

2. Which of the following food items would interfere with your Coumadin (warfarin) medication?
a. Bacon
b. Broccoli*
c. Bananas
d. Peeled cucumbers

3. While on Coumadin (warfarin) medication, in which of the following would you go directly to the emergency room?
a. Small bruises
b. Your appetite dramatically increases
c. Nosebleed which will not stop bleeding*
d. Gums which bleed for a few seconds after brushing teeth

4. You just remembered that you forgot to take your evening Coumadin (warfarin) medication dose last night. You would ____
a. skip the dose of Coumadin (warfarin) you missed*
b. take the missed Coumadin (warfarin) dose right now
c. wait and take 2 doses of Coumadin (warfarin) this evening
d. take one-half of the missed dose of Coumadin (warfarin) right now

5. While on Coumadin (warfarin) you _____
a. should not eat spinach
b. can eat spinach one time a month
c. can eat as much spinach as you would like whenever you would like
d. can eat spinach but need to eat the same amount regularly every week*

6. While out with friends for dinner, you have just finished your third glass of wine. This amount of alcohol consumed in a single evening will
a. cause a decrease in your INR
b. cause an increase in your INR*
c. not affect you or your Coumadin (warfarin) in any way
d. make you sick when taking Coumadin (warfarin) medication

7. While in your pharmacy, you notice multivitamins are on sale. After some thought, you decide that you may need a multivitamin. You would _____
a. purchase the multivitamin and begin taking it regularly
b. not take a multivitamin because it will cause a blood clot while taking Coumadin (warfarin)

c. start taking it and bring the multivitamin to your next Coumadin Clinic visit to show the pharmacist
d. purchase the multivitamin but not start taking it until you talked with the pharmacist at your Coumadin Clinic*

8. If you ran out of your prescription for your Coumadin (warfarin) you would _____
a. borrow Coumadin (warfarin) from a friend, as long as it is the same dose as yours
b. call and ask for refills for that day so you do not miss a dose of Coumadin (warfarin)*
c. wait until your next appointment that is just a few days away to get a new prescription
d. do nothing because you have taken Coumadin (warfarin) long enough, otherwise there would be more refills on your prescription

9. Which of the following is an effect of Coumadin (warfarin) medication that will most likely be experienced?
a. Stroke
b. Leg clot
c. Bruising*
d. Blood in the urine

10. You have a cold, which includes a runny nose and a cough. You _____
a. could safely take Nyquil to help get rid of the runny nose and cough
b. take your friend's medication that he/she uses for a bad cold because he/she is also on Coumadin (warfarin) medication
c. would call the Coumadin Clinic and tell him/her you are on Coumadin (warfarin) medication and ask what you can take for your cold*
d. decide it is safer to suffer through the cold because most cold medications will interact with your Coumadin (warfarin) medication

11. When making a dental appointment while taking Coumadin (warfarin) medication, you need to remember you ____
a. cannot have procedures done on your teeth while taking Coumadin (warfarin)
b. must tell your dentist you are taking Coumadin (warfarin) well in advance of having any procedure done*
c. can have procedures done and there is not a need to tell the dentist about the Coumadin (warfarin)
d. can have the dental procedure done if when you arrive at your dental appointment you tell the dentist you are taking Coumadin (warfarin)

12. When the need arises to take an antibiotic (to get rid of an infection) while taking Coumadin (warfarin), you need to _____
a. take half of the prescribed length of therapy, and then call the Coumadin Clinic
b. refuse to take any new medication because you are taking Coumadin (warfarin)
c. wait until your next Coumadin Clinic visit and then tell the pharmacist about the antibiotic
d. call the Coumadin Clinic right away and let them know you are starting a new medication*

13. Coumadin (warfarin) works _____
a. in my liver to make my blood thicker
b. in my liver to make my blood thinner*
c. in my kidneys to make my blood thicker
d. in my kidneys to make my blood thinner

14. The best time of day for me to take my Coumadin (warfarin) is _____
a. at lunchtime
b. in the evening*
c. in the morning before breakfast
d. any time of day when I remember

15. Which of the following is an effect of my Coumadin (warfarin) medication that I will most likely experience if my INR is too high?
a. A clot in the leg
b. Minor bleeding*
c. Clot in the lung
d. Bleeding in the brain

16. Which of the following drinks can decrease the effectiveness of your Coumadin (warfarin)?
a. 2% low-fat milk
b. Chocolate shake
c. Orange juice
d. Ensure nutritional supplement*

17. While taking Coumadin (warfarin), which of the following represents a situation when you should to go to the emergency room?
a. You cough up blood*
b. Your nose bleeds slightly while blowing it
c. You gums bleed after brushing your teeth then it stops quickly
d. You have cut yourself while shaving and you control the bleeding

18. Your neighbour brings over this great ‘‘all natural’’ herbal supplement she just bought from her chiropractor. She swears that this helps all her aches and pains and recommends that you take it when you ache. Your decision is to _____
a. take her advice, realizing that you could use this herbal supplement
b. start taking the herbal supplement and tell your pharmacist at the next office visit
c. ask your pharmacist if the herbal supplement will interact with your medications before you take it*
d. avoid taking herbal supplements altogether because all medications interact with Coumadin (warfarin)

19. Once you have reached a stable Coumadin (warfarin) dose, a PT/INR blood test _____
a. should be checked once a year
b. should be checked once every 3 months
c. should be checked at least once every 4 weeks*
d. does not need to be checked once you are on a stable Coumadin (warfarin) dose

20. The results of your PT/INR test tells the pharmacist
a. how thick or thin your blood is while taking Coumadin (warfarin)*
b. how well your kidneys are working since taking Coumadin (warfarin)
c. what your average blood sugar level was since taking Coumadin (warfarin)
d. how much alcohol you have been drinking since taking Coumadin (warfarin)

21. While taking Coumadin (warfarin), you should call your Coumadin Clinic when you get:
a. a backache
b. an upset stomach
c. a tension headache
d. diarrhea for more than 1 day*

22. While on Coumadin (warfarin) you need to be routinely monitored for which of the following:
a. PT/INR tests*
b. Potassium levels
c. Blood glucose levels
d. Kidney function tests

23. Which of the following may have a significant effect on how well your Coumadin (warfarin) works?
a. Changes in your mood
b. Changes in sleep habits

c. How much water you drink
d. Using over the counter medications*

24. While taking Coumadin (warfarin), which of the following should lead you to the emergency room?
a. Loss of appetite
b. Brown loose stools
c. Urine becomes red in color*
d. A quarter size bruise on your arm

25. Which of the following foods could affect how well your Coumadin (warfarin) works?
a. Celery
b. Carrots
c. Cole slaw*
d. Green beans

26. You have generic and brand Coumadin (warfarin) tablets at home that are both the same dose. You should _____
a. take both because they work differently
b. take only brand or only generic, but not both*
c. not take either until you call the Coumadin Clinic
d. alternate days by taking brand on one day and generic on the next day

27. Once your Coumadin (warfarin) is stopped, how long does it take to get the medication to get out of your system?
a. 5 hours
b. 5 days*
c. 5 weeks
d. 5 months

28. After starting Coumadin (warfarin), how long (in months/years) would you expect to be taking Coumadin (warfarin)?
a. 1 year
b. 1 month
c. It depends on each person's needs*
d. If you start Coumadin (warfarin), you will have to be on the medication for the rest of your life

29. Which of the following activities are more risky while taking Coumadin (warfarin)?
a. Playing football, because you can hit your head*
b. Taking a bath, because soap interacts with Coumadin (warfarin)
c. Playing cards because using your hands a lot will cause a blood clot
d. Walking a lot, because exercise is not good for you while taking Coumadin (warfarin)

Adapted from
A.L. Briggs et al. / Research in Social and Administrative Pharmacy 1 (2005) 40–59

2. Dietary Questionnaire K-CARD

Patient ID _____ Date of Completion_____

Please select the time frame that this questionnaire applies to
[ ] Baseline [ ] Month 4
[ ] Month 2 [ ] Month 6

Please indicate which foods you eat on each day of the following week. If you eat more or less than one serving, please indicate how much. *For example, one (1) serving of brussel sprouts is shown in the chart to be ½ cup. If, on Sunday, you had one (1) cup of brussel sprouts (which counts as two (2) servings) then you would mark "2" under the box where Sunday and Brussel Sprouts intersect.*

If you have any trouble filling out this form please contact Habeeb Majeed (613) 798-5555 ext 13805

Food	One Serving	Sun	Mon	Tues	Wed	Thurs	Fri	Sat	Weekly Total
Meat/Poultry/Fish									
Chicken (fried)	3 oz. (1/2 breast)								
Chicken Nuggets	6 nuggets								
Fish Sticks	3 sticks								
Tuna, canned in oil	3 oz.								
Fruits/Vegetables									
Asparagus	4 spears								
Avocados	½ small (6-8 slices)								
Blackberries	1 cup								
Blueberries	1 cup								
Bok-Choy (Chinese Cabbage)	1 cup								
Broccoli	1 cup (6 spears)								
Brussel Sprouts	½ cup								
Cabbage	1 cup								
Cauliflower	1 cup								
Chick Peas/garbanzo (hummus)	½ cup								
Coleslaw (with dressing)	½ cup								
Celery	1 stalk								
Cucumber with peel	½ cup								
Endive	1 cup								
Grapes, red or green									
Greens (Collard)	1 cup								
Greens (Turnip/mustard)	1 cup								
Green Beans	½ cup								

Food	One Serving	Sun	Mon	Tues	Wed	Thurs	Fri	Sat	Weekly Total
Green Peas	1 cup								
Kale	1 cup								
Kiwi fruit (or Chinese gooseberry)	1 medium								
Lettuce	1 cup								
Mixed vegetables	½ cup								
Parsley	10 sprigs								
Potato (French fries)	10 fries								
Prunes (dried plums)	6 prunes								
Rhubarb	½ cup								
Sauerkraut	¼ cup								
Scallions (spring onions)	½ cup								
Spinach	1 cup								
Okra	½ cup								
Peas, green	1 cup								
Peas, Blackeye	1 cup								
Beverages									
Carrot Juice	1 cup (6 oz.)								
Soy Milk	1 cup (6 oz)								
V8 Juice	1 cup (6 oz)								
Green Tea	1 cup (6 oz)								
Mixed Dishes/Prepared Meals/ Desserts									
Beef Chow Mein (Chinese)	1 cup (6 oz.)								
Cake/Brownies	1 (2 in' square)								
Cookies	1 medium								
Crackers	6 crackers								
Danish/Doughnut	1 medium								
Egg Noodles	1 cup								
Macaroni and Cheese	1 cup (6 oz)								
Muffin	1 medium								
Pasta Sauce (Spaghetti/marinara)	1 cup (6oz.)								
Pie	1 slice (1/8 large)								
Pizza, cheese	1 slice (1/8 large)								
Popcorn (popped in oil)	2 cups (2 oz)								
Potato Chips	1 cup (1 oz)								
Soybean (tofu)	½ cup								
Spinach Souffle	6 oz.								
Fats/Oils/Dressings									
Mayonnaise									
Olive Oil	1 tbsp								

Food	One Serving	Sun	Mon	Tues	Wed	Thurs	Fri	Sat	Weekly Total
Salad dressing, blue or roquefort cheese dressing	1 tbsp								
Salad dressing, French dressing	1 tbsp								
Salad dressing, vinegar and oil	1 tbsp								
Fast Food									
Burger King, Chicken *Whopper* Sandwich	1 sandwich								
Burger King, Original Chicken Sandwich	1 sandwich								
Burger King, *Double Whopper* Sandwich	1 sandwich								
Burger King, *Whopper* Sandwich	1 sandwich								
Wendy's Classic Single	1 sandwich								
Wendy's *Homestyle* Chicken Filet sandwich	1 sandwich								
Wendy's Ultimate Chicken Grill Sandwich	1 sandwich								
Supplements									
Products containing Vitamin K	≥25 mcg								
High dose Vitamin C	1000 mcg								
High Dose Vitamin E	1000 mcg								
Alcohol									
Beer	12 fl oz.								
Wine (red and white)	3.5 fl oz.								
Spirits, all (gin, rum, vodka, whiskey, etc…)	1.5 fl oz.								

If there are any foods which you are unsure about, please feel free to write them down in the space below to discuss with the research associate during your next phone call/visit

3. Brief Medication Questionnaire (BMQ)

Patient ID __ __ __ __

During the **PAST WEEK**, please answer the following questions about **WARFARIN**

a) How many days did you take it _____
b) How many times per day did you take it _____
c) How many pills did you take each time
   - Sunday _____
   - Monday _____
   - Tuesday _____
   - Wednesday _____
   - Thursday _____
   - Friday _____
   - Saturday _____

d) How many times did you miss taking a pill _____

Below is a list of problems people can have with their medication, please indicate (X) how hard it is for you to do the following with **WARFARIN**

	Very Hard	Somewhat Hard	Not Hard at all
a) Open or close the medication package	_____	_____	_____
b) Read the print on the medication package	_____	_____	_____
c) Remember to take all the pills	_____	_____	_____
d) Get your refills in time	_____	_____	_____
e) Taking multiple pills at the same time	_____	_____	_____

How well does the medicine work for you (1= Well, 2=Okay, 3= Not Well) _____

Does the WARFARIN Bother You in Any Way? Yes ___ No ____

If YES, please check below how much it bothers you
A lot _____ Some _____ A little ____ Never _____

In what way did it bother you _____

4. Concomitant Medications Form For Baseline Visit

Patient ID __ __ __ __

Data Collection Date __ __ __ __ __ __ __ __

D D M M Y Y Y Y

Current Medications (including dosages) that is currently being taken by the patient:

To Research Associate, please take note of the following potentially interacting medications:

Antibiotics
Ciprofloxacin (Cipro, Ciprobay, Ciproxin)
Co-trimoxazole (Septra, Septrin, Bactrim)
Erythromycin
Isoniazid
Metronidazole
Amoxicillin/clavulanate
Azithromycin
Clarithromycin
Levofloxacin
Lopinarvir
Ritonavir
Tetracycline
Griseofulvin
Nafcillin
Ribavirin
Rifampin
Dicloxacillin

Antifungals
Fluconazole
Isoniazid
Metronidazole
Miconazole oral gel
Miconazole vaginal suppositories
Voriconazole
Itraconazole

Antidepressants
Fluvoxamine
Sertaline
Citalopram
Disulfram
Entacapone
Anti-lipid
Fluvastatin
Fenofibrate
Simvastatin
Cholestyramine
Anti-Arrhythmic
Amiodarone
Clofibrate
Diltiazem
Propafenone
Propranolol
Sulfinpyrazone
Quinidine
Ropinirole

Anti-inflammatory, Analgesic
Acetaminophen (regular use)
Aspirin (regular use)
Piroxicam
Dextropropoxyphene
Celecoxib
Rofecoxib
Interferon
Tramadol
Herbal Supplements
Boldo-fenugreek
Quilinggao
Danshen/methyl salicylate
Dong quai
Lycium barbarum L (Chinese Wolfberry)
PC-SPES
Ginseng
St.John's Wort
Fish Oil supplements
Vitamin C supplements
Vitamin E supplements

5. Concomitant Medications Form For Followup

Patient ID __ __ __ __

Data Collection Date __ __ __ __ __ __ __ __

D D M M Y Y Y Y

Please select the time frame that this questionnaire applies to

[ ] Month 1 [ ] Month 4
[ ] Month 2 [ ] Month 5
[ ] Month 3 [ ] Month 6

Have there been any changes to the number of prescription medications the patient is taking.
[ ] Yes [ ] No Number of prescription medications _____

Has there been any changes to potentially interacting medications since the last measurement
[ ] Yes [ ] No

Please present all the medications the patient is taking (include dosage)

To Research Associate, please take note of the following potentially interacting medications:

Antibiotics
Ciprofloxacin (Cipro, Ciprobay, Ciproxin)
Co-trimoxazole (Septra, Septrin, Bactrim)
Erythromycin
Isoniazid
Metronidazole
Amoxicillin/clavulanate
Azithromycin
Clarithromycin
Levofloxacin
Lopinarvir
Ritonavir
Tetracycline
Griseofulvin
Nafcillin
Ribavirin
Rifampin
Dicloxacillin

Antifungals
Fluconazole
Isoniazid
Metronidazole
Miconazole oral gel
Miconazole vaginal suppositories
Voriconazole
Itraconazole

Antidepressants
Fluvoxamine
Sertaline
Citalopram
Disulfram
Entacapone
Anti-lipid
Fluvastatin
Fenofibrate
Simvastatin
Cholestyramine
Anti-Arrhythmic
Amiodarone
Clofibrate
Diltiazem
Propafenone
Propranolol
Sulfinpyrazone
Quinidine
Ropinirole

Anti-inflammatory, Analgesic
Acetaminophen (regular use)
Aspirin (regular use)
Piroxicam
Dextropropoxyphene
Celecoxib
Rofecoxib
Interferon
Tramadol
Herbal Supplements
Boldo-fenugreek
Quilinggao
Danshen/methyl salicylate
Dong quai
Lycium barbarum L (Chinese Wolfberry)
PC-SPES
Ginseng
St.John's Wort
Fish Oil supplements Vitamin C supplements
Vitamin E supplements