Implementation of a Computerized Decision Support System for Warfarin Dosing in Hemodialysis Patients: A Study of Effectiveness and Safety

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1.0 ABSTRACT

Statement of the problem: The risk-benefit profile of warfarin anticoagulation in hemodialysis (HD) patients differs compared to the non-HD population. Computerized decision support systems (CDSS) to assist with anticoagulation management are safe and effective in the non-HD population but had not previously been studied in HD outpatients.

Methods of investigation: A before – after study compared anticoagulation control during pre-existing, nephrologist-led anticoagulation management to that following implementation of a pharmacist-led, CDSS-assisted strategy, in HD patients on warfarin at The Ottawa Hospital.

Results: Forty-two patients were included. Following implementation of the CDSS-assisted strategy, median time-in-range increased by 3.7% (IQR, -9.5% - 20.6%; p = 0.247). Median frequency of INR tests per day decreased: -0.040 (IQR, -0.074 to –0.0008; P = 0.0001). Adverse events were similar.

Conclusion: A CDSS-assisted strategy for anticoagulation management in HD patients is effective, safe and may lead to cost savings related to less frequent INR testing.

2.0 BACKGROUND AND LITERATURE REVIEW

2.1 Therapeutic Use of Warfarin for Anticoagulation

Warfarin is an oral medication used to provide therapeutic anticoagulation in a variety of clinical settings (1, 2). The medical use of warfarin to prevent and treat thrombosis began in the 1950s (3) and it remains the standard oral anticoagulant in clinical use today (2). Although widely used, the pharmacological characteristics of warfarin are such that careful laboratory monitoring is required for its safe clinical use. In the following sections, the pharmacology and clinical uses of warfarin are briefly reviewed.

2.1.1 Pharmacology of Warfarin

Warfarin is the prototypical Vitamin K antagonist (VKA) medication. Other VKAs such as phenprocoumon, fluindione and acenocoumarol are biologically similar but have different biological half-lives. The biological half-life of warfarin is 36 to 42 hours whereas the half-lives of phenprocoumon and fluinidione are much longer, approximately 96 hours and 69 hours respectively (1, 4-6). In contrast, the biological half-life of acenocourarol is significantly shorter than Warfarin's (approximately 9 hours) (4, 5).

VKAs reduce blood clotting (thrombogenesis) by inhibiting Vitamin K-dependent gamma-carboxylation of coagulation factors II, VII, IX, and X (which are known as the 'Vitamin K-dependent clotting factors') (1, 7). This results in a proportion of the Vitamin K-dependent clotting factors being produced by the liver to be biologically inactive (7, 8). As a consequence, Vitamin K levels and metabolism regulate the degree to which warfarin is effective in exerting its pharmacologic effects. Through the same Vitamin-K

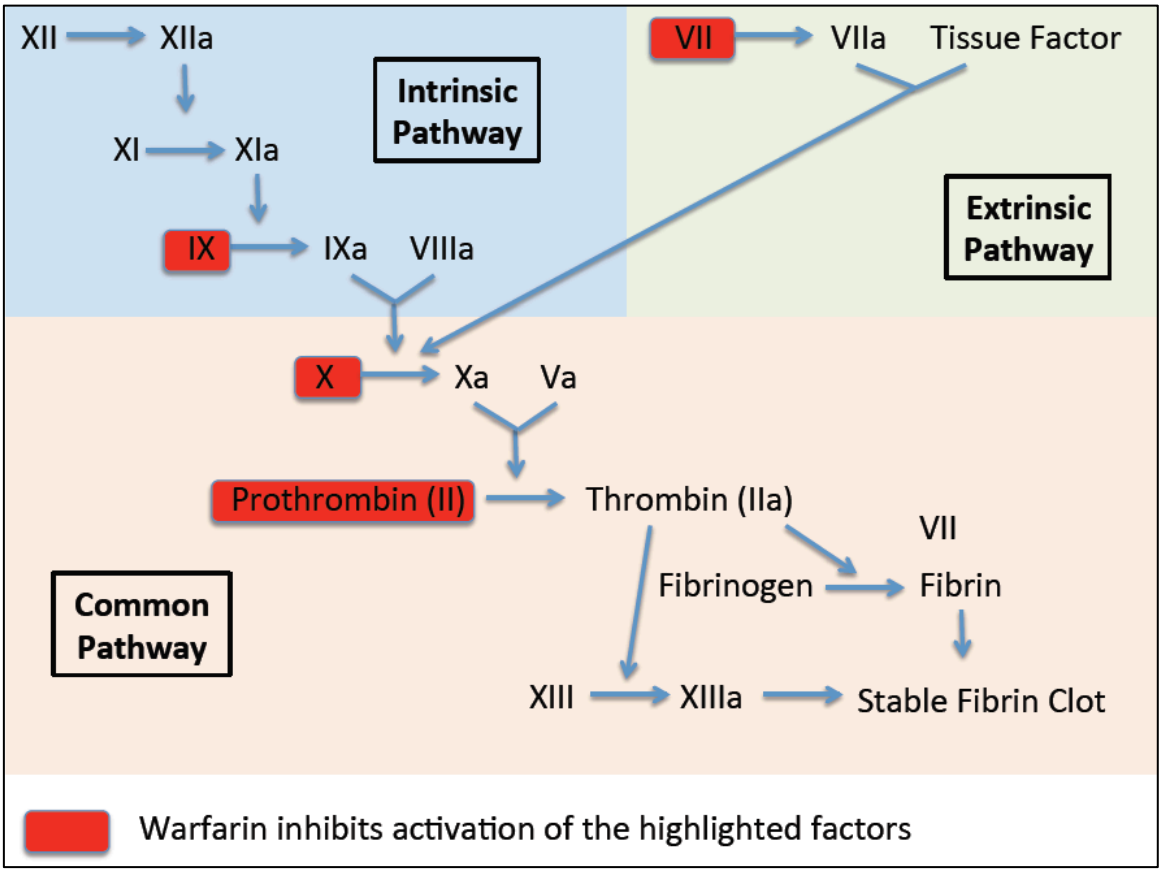
dependent pathway, Protein C and Protein S---intrinsic anticoagulants found in the circulation---are also inhibited by VKAs (9). Thus, paradoxically, VKAs may promote thrombogenesis (clotting) and anticoagulation (blood thinning) through the same mechanism (9). While the balance between the thrombogenic and anticoagulant actions of warfarin both contribute to determining the overall level of anticoagulation at any particular time-point, ultimately, the effect of reduced levels of clotting factors predominates and results in anticoagulation (1).

The speed with which an oral medication is absorbed can also influence the time of onset of action however commercially available forms of warfarin for medical use are water soluble and entirely absorbed soon after oral administration (1). Oral warfarin consists of a racemic mixture of both R and S enantiomers (1). The S enantiomer is more potent biologically and is metabolized by the CYP2C9 microsomal system in the liver (1). Because the CYP2C9 enzyme system is involved in the metabolism of multiple other medications, concurrent use of these medications affects warfarin metabolism (10-16). Only the non-protein-bound portion of warfarin in the bloodstream is biologically active and since it is strongly protein-bound (mainly to serum albumin), other drugs that bind protein (and albumin, in-particular) can displace it into the biologically active fraction (8). Thus, the presence of other drugs and the rate of normal albumin synthesis in the liver can both influence the biologic activity of warfarin. Notably, excretion of warfarin is through the urine with most of the drug being excreted after having been metabolized (8).

Although the biological half-life of any drug may be affected by patient-specific factors, it typically takes approximately five or six half-lifes before a drug reaches steady-state concentration (17). The biological half-life of warfarin is 36 to 42 hours (5, 6). As such,

with initiation of treatment, there is no immediate or even short-term loss of significant clotting factor activity since the action of warfarin inhibits the synthesis of new active clotting factors as opposed to inhibiting those that are already formed (1, 7). This means that the half-life of existing clotting factors also determines the time that it takes for anticoagulation to occur after initiation of treatment with warfarin or other VKAs (18). Normal thrombogenesis occurs through activation of either the intrinsic and extrinsic coagulation pathways (or both) and their shared final common pathway (1, 7).

Figure 1: The coagulation cascade and sites of Warfarin inhibition. Adapted from Ferguson *et al*. (1998) (19).



The half-life of factor II (also called 'prothrombin'), which is an essential component of the intrinsic coagulation pathway, is approximately 3 days so the effect of warfarin is delayed for some time after initiation of treatment (18). During the initial period of treatment with warfarin, the extrinsic coagulation pathway is most affected since it works through the activation of factor VII, the Vitamin K dependent clotting factor with the shortest half-life (4 to 6 hours) (20). Since the other Vitamin K-dependent factors have longer half-lives and are involved in the intrinsic and common coagulation pathways, full anticoagulation does not occur until the levels of these other factors (such as factor II / prothrombin, as described above) are markedly reduced. Early inhibition of only the extrinsic pathway may prolong the prothrombin time, a laboratory measure of anticoagulation (discussed in more detail below) prior to the occurrence of actual anticoagulation (20).

The biological half-lives of the intrinsic anti-coagulants Protein C and Protein S, whose production is also inhibited by warfarin, are relatively short compared to the clotting factors, being less than 15 minutes (21) and 42.5 hours (22), respectively. As such, there is a paradoxical, theoretical, small increased risk of thrombosis at the time of starting warfarin treatment (1, 20). Typically, therapeutic anticoagulation with warfarin is achieved less than one week after starting treatment (1, 18). At that point, the Vitamin-K dependent factors are predominantly (65-90%) in the inactive form and in equilibrium with functional clotting factors that are still also being produced by the liver (1).

The somewhat complex pharmacological properties of warfarin, as briefly summarized above, explain why Warfarin's anticoagulant effect requires careful monitoring while initiating and maintaining therapeutic anticoagulation in clinical practice.

2.1.2 Laboratory Monitoring of Anticoagulation

The laboratory test most commonly used to monitor the therapeutic effect of Warfarin is the prothrombin time (PT). The PT is prolonged when there is reduced activity of the clotting factors II, VII and X but is not affected by decreased factor IX activity (23). As such, the PT assesses the extrinsic (and common) pathway of clotting.

PT testing is performed by the addition of calcium (necessary for clotting factor activity) to a citrated plasma sample from the patient (citrate binds calcium present at the time of blood collection rendering clotting factors inactive) after having added thromboplasin (tissue factor) (24). The PT is the time (in seconds) that it takes for a fibrin clot to form, as detected using either optical, electromechanical or visual means (24).

For monitoring warfarin therapy, it is recommended by the World Health Organization that the results of PT testing be expressed as the International Normalized Ratio (INR) (23). This recommendation stemmed from historical difficulties in standardizing the thromboplastin used in various labs to do PT testing (23). To allow PT testing for warfarin monitoring to be comparable across laboratories locally and internationally, the WHO developed a recombinant thromboplastin to be used as a reference standard (23). The International Sensitivity Index (ISI) is determined for each individual lab's PT reagent and instrument combination and is defined relative to that determined using a recombinant thromboplasin that is the international reference standard (23). As such, the INR accounts for inter-laboratory variation in the sensitivity of PT testing reagents to the effects of warfarin according to the following formula:

$$INR = [\text{Patient PT} / \text{Control PT}]^{ISI}$$

The control PT is determined in each laboratory as the mean PT of 30 (or more) normal plasma samples handled exactly as a patient sample is usually handled (23).

Since a properly collected blood sample forms the basis for accuracy of any coagulation testing, it is important that initial blood samples are free of tissue fluids, heparin or other IV solutions delivered through intravenous lines. This is an important consideration when blood samples are obtained from hemodialysis (HD) catheters (25). It should be noted that heparin, an intravenous anticoagulant (commonly used during HD treatments to maintain the patency of vascular access) does not typically prolong the PT since the testing reagents typically are heparin-neutralizing (26). Nonetheless, the PT may be transiently prolonged after a bolus administration of heparin in which the concentration of heparin overwhelms the heparin-neutralizing materials in the testing reagents (26).

2.1.3 Indications for Anticoagulation with Warfarin

In general, therapeutic anticoagulation is used to prevent or treat thromboembolic events and complications. Indications for sustained anticoagulation with warfarin include (27):

- **Atrial fibrillation and atrial flutter**

  Atrial fibrillation and atrial flutter are related pathologic cardiac dysrhythmias (conditions defined by an irregular heart beat) that predispose to the formation of emboli (clots) on the heart valves or within the left ventricle (28-30). These emboli may then dislodge and migrate up the carotid arteries resulting in an ischemic cerebrovascular accident (CVA) (or stroke) (2). Through the same

mechanism, atrial fibrillation is also a major risk factor for systemic embolism due to migration of emboli through other arteries than the carotids (2).

There is strong evidence that, in the context of atrial fibrillation, therapeutic anticoagulation with warfarin reduces the future risks of CVA and systemic thromboembolism (31-33). The 2008 Canadian Best Practice Recommendations for Stroke Care includes a recommendation that "for primary prevention of stroke in patients with atrial fibrillation, acetylsalicylic acid (ASA) or anticoagulation with warfarin should be considered based on the clinical circumstances" (33). Since different individuals with atrial fibrillation will have a different risk of having a subsequent thrombotic event relative to their risk of having a complication related to anticoagulation therapy (either ASA or a VKA such as Warfarin), the determination of what, if any, antithrombotic therapy is indicated for an individual patient hinges on whether or not the risk of a thrombotic event outweighs the increased risks of bleeding or other complications of antithrombotic therapy for that particular individual. In order to guide the clinical decision making process in this regard, at least 12 different multivariate risk scoring-systems have been developed (34). The CHADS2 score (35) has been the most widely used of these scoring systems, largely due to its simplicity and consequent ease of use in clinical practice (36).

Table 1: CHADS2 Scoring System (35)

Clinical Variable	**Points**
Congestive Heart Failure (CHF)	1
Hypertension (previous history)	1
Age ≥75 years	1
Diabetes mellitus	1
Secondary prevention in those with a prior ischemic CVA or TIA	2

The CHADS2 score correlates with the risk of future CVA (but does not consider transient ischemic attacks (TIAs)) (36). Those with a score of 0 are considered 'low risk', 1 or 2 is 'moderate risk' and 3 or more is high risk.

The risk of future CVA correlates strongly with CHADS2 scoring. At all CHADS2 scores of 1 or more, the risk of subsequent CVA is significantly more likely for those who are not on warfarin. For those with a score of 0, the same trend has been observed but was not statistically significant in a study of 11,528 patients in Northern California with non-valvular (i.e. no cardiac valve disease on echocardiogram) atrial fibrillation that was used to derive the following table (36):

Table 2: CHADS2 Score and Future Risk of Cerebrovascular Accident

CHADS2 Score	CVAs per 100 person-years	
	Warfarin	**No Warfarin**
0	0.25	0.49
1	0.72	1.52
2	1.27	2.50
3	2.20	5.27
4	2.35	6.02
5 or 6	4.60	6.88

The number needed to treat (NNT) to prevent a CVA was found to be 417 for those with a CHADS2 score of 0. For those with a CHADS 2 score of 5 or 6, the NNT was 44 (36). In general, it is recommended (32) that those with a CHADS2 score of 2 or more be considered for oral anticoagulation with a VKA after the diagnosis of atrial fibrillation. For those with a score of 0, anticoagulation is not typically recommended. Those with a score of 1 are at intermediate risk and may be treated with oral anticoagulation using a VKA or with aspirin (ASA) depending on the individual clinical circumstances: patients more concerned about the risk of stroke than the risk of bleeding should be considered for anticoagulation with a VKA in the absence of other considerations. It should be noted that the decision to start a patient on oral anticoagulation with a VKA must also include consideration of an individual's risk of bleeding or other complications related to VKA therapy (32).

- **Prosthetic heart valves**

  Due to a high risk of thromboembolism (including CVA and other embolic events), anticoagulation with a VKA is recommended for all patients with mechanical heart valves and for selected 'high-risk' patients with bioprosthetic

heart valves (37-39). A systematic review and meta-analysis of observational studies and RCTs that were published between 1970 and 1992 assessed the risks and benefits of anticoagulation in patients with mechanical heart valves (40). This review included 46 studies with 13,088 patients in total (for 53,647 patient-years of data) (40). Major embolic events were defined as those which caused death, left a residual neurologic deficit (i.e. CVA) or resulted in persistent peripheral ischemia (40). The risk of a major embolic event for those who were not treated with a VKA was 4.0 events per 100 patient years (40). In contrast, the rate was only 1.0 events per 100 patient years for those treated with a VKA (40). Subsequent large studies have shown similar rates of thromboembolic events for treated and untreated patients with mechanical valves (41, 42).

In addition to preventing embolic events, the risk of mechanical valve thrombosis was found to be 1.8 per 100 patient years for those untreated with a VKA compared to 0.2 per 100 patient years for those who were treated (40). The restrictive definition of valve thrombosis used for the review (i.e. thrombus limiting valve function and diagnosed at time of surgery or autopsy) probably led to an underestimate in the frequency of valve thrombosis being captured as an event (40).

Another interesting finding of this review were that the risks of adverse events were significantly increased for those with mitral as opposed to aortic mechanical valves (40). As well, the risk of major bleeding in those treated with VKA therapy was found to be 1.4 events per 100 patient years of follow-up (40). A subsequent study of 1608 patients with 6475 patient-years reported the rate of major bleeding

to be 2.6 per 100 patient-years of follow-up (41).

There are several important limitations to the abovementioned review. First, observational studies and RCTs were included together and it is likely that the observational studies had inadequate reporting of events. As well, since anticoagulation became the standard-of-care over the course of the period for which studies were included, the oldest studies were used to determine the rates of adverse events without anticoagulation using a VKA. At the same time, the mechanical valves used at the time of the older studies are known to be more thrombogenic than those used today (38). Nonetheless, the risks of thromboembolism and valve thrombosis without VKAs so dramatically outweigh the risks of bleeding with VKAs that there is clear evidence to support the recommendations of the American College of Cardiology/American Heart Association (37), the American College of Chest Physicians (39) and the European Society of Cardiology (38) that all those with a mechanical valve undergo long-term anticoagulation with a VKA.

- **Deep vein thrombosis, pulmonary embolus (or other venous thromboembolism (VTE))**

  There is a strong evidence base to support the use of anticoagulation therapy for the prevention and treatment of *de novo* and recurrent venous thromboembolic disease (43, 44). While the duration of therapy may vary according to the clinical situation, it is recommended that VKAs be used for anticoagulation that is required beyond the acute period of the presentation of VTE disease unless clearly contraindicated (43, 44).

- **Antiphospholipid antibody syndrome (APAS)**

  APAS is an autoimmune condition that results in hypercoagulability. In order to prevent future or recurrent venous and arterial thromboembolic events, treatment those with APAS typically includes long-term anticoagulation, usually with VKAs (2, 45, 46).

- **Anterior myocardial infarction with left ventricular thrombus or high risk for left ventricular thrombus**

  Those considered at high risk of ventricular thrombus are those with an ejection fraction less than 40%, anteroapical wall motion abnormality (2). If a thrombus is present or there are risk factors, anticoagulation with a VKA is indicated to prevent embolic phenomena related to clot migration (2).

- **Maintaining HD catheter patency**

  Vascular access has been referred to as the 'Achilles heel' of HD therapy. For the group of HD patients dialysed using a HD catheter (as opposed to an arteriovenous fistula or graft), the most frequent complication of HD is catheter dysfunction (i.e. poor blood flow) (47).

  HD catheter dysfunction is defined as 'early' or 'late' (48): 'early' is that which occurs immediately following catheter placement and is usually a technical issue whereas 'late' occurs after a period in which the catheter functioned well and is generally due to partial or complete thrombosis of the catheter.

  There have been several studies suggesting that the use of warfarin at a dose that does not significantly increase the INR (i.e. 1 mg daily) improves the patency of CVCs used to treat patients with a hematologic malignancy (49, 50).

Unfortunately, a randomized trial of 105 chronic HD patients with tunneled HD catheters showed no significant effect of this strategy on thrombosis-free catheter survival or time to the first use of a thrombolytic instillation (the use of a 'clot-busting' drug within the catheter) (51).

Some observational studies suggest that therapeutic anticoagulation with Warfarin may reduce late HD catheter dysfunction (52-54). One retrospective study of 65 HD patients showed that the thrombosis rate for 35 patients with a history of prior 'late' catheter dysfunction who were started on warfarin with a target INR of 1.5 to 2.0, was 0.03 thrombotic events per 100 catheter days compared to 0.13 events per 100 catheter days for 30 controls without a past history of 'late' catheter dysfunction and not on warfarin ($p = 0.01$) (52). Another study reported significantly improved HD catheter patency by using warfarin to target an INR of 1.5 to 2.0 in patients considered to be at high risk of late catheter dysfunction (54). Similarly, an observational study of 48 HD patients who had previously been treated with a thrombolytic instillation for catheter dysfunction showed improved long-term HD catheter patency using warfarin to maintain an INR of 2.0 to 2.5 (53).

While these studies suggest that there may be a role for systemic anticoagulation in HD patients at high risk of 'late' catheter dysfunction due to recurrent thrombosis, to date, no controlled prospective studies have been reported. As such, the evidence base to suggest the routine clinical use of Warfarin anticoagulation in this context is weak.

Table 3: Target INR and Target INR Range For Common Indications for Anticoagulation

Indication for Anticoagulation	**Target INR**	**Target INR Range**	**Reference(s)**
Atrial fibrillation or atrial flutter (with moderate to high risk of CVA)	2.5	2 to 3	(44, 55)
Anterior myocardial infarction with left ventricular thrombus or at high-risk of left ventricular thrombus (i.e ejection fraction <40%, anteroapical wall motion abnormality)	2.5	2 to 3	(44)
Mechanical aortic valve	2.5	2 to 3	(44)
Mechanical mitral valve	3	2.5 to 3.5	(44)
Biprosthetic mitral valve (for first three months following insertion)	2.5	2 to 3	(44)
Specific, older mechanical aortic valves (i.e. caged ball or caged disk-type)	3	2.5 to 3.5	(56)
Venous thromboembolism (for 3 months duration if related to a reversible, transient risk factor (e.g. prolonged immobilization); for at least 3 months or more for an unprovoked event; extended anticoagulation in the context of hypercoagulability (e.g. cancer, genetic predisposition)	2.5	2 to 3	(44)
Antiphospholipid antibody syndrome	2.5	2 to 3	(44)
Prevention of 'late' hemodialysis catheter dysfunction	1.75	1.5 to 2	(54)
	2.25	2 to 2.5	(53)

2.1.4 Factors Influencing the Dose-Response to Warfarin

Since there is a real danger that 'over-anticoagulation' with Warfarin treatment can lead to bleeding complications and 'under-anticoagulation' is ineffective in treating or preventing of thromboembolic complications, it is important to understand the multiple factors that can affect an individual patient's dose-response to Warfarin. The following section discusses some of the reasons why a standardized dose of Warfarin may affect individual patients differently in terms of the degree of anticoagulation achieved with a given dose of the medication.

Genetic Factors

Genetic polymorphisms for three enzymes have been found to be associated with variable responses to warfarin dosing (10-16, 18, 57-59):

- Cytochrome P-450 2C9 (CYP2C9): this is a hepatic enzyme that is involved in the metabolism of warfarin and many other medications. This enzyme normally acts to inactivate warfarin (and other VKAs) (60-63). Subjects with genetic variants to the wild-type allele have been shown in multiple studies to have an increased sensitivity to warfarin (i.e. lower doses result in a relatively greater degree of anticoagulation) (60, 64, 65). Consistent with this finding, those with at least one variant (non-wild-type) allele have also been shown to take a longer time to have a stable dose of warfarin (or other VKA) established for maintenance of a therapeutic level of anticoagulation (60, 64-69).
- Cytochrome P-450 4F2: the precise mechanism by which this enzyme affects warfarin (or Vitamin K) metabolism is unknown however a variant allele has been

associated with relatively higher warfarin dose requirements (4 to 12% increased doses) to achieve therapeutic levels of anticoagulation than for subjects with a more-common allele variant (57). A separate study made similar findings with respect to the dosing of acenocoumarol for patients with this particular variant allele (58).

- Vitamin K epoxide reductase complex 1 (VKORC1): genetic variation in the coding for this enzyme involved in Vitamin K metabolism has been shown to be associated with variable dose-responses to warfarin therapy (16, 70, 71). One study demonstrated that subjects with a 'group A' haplotype required significantly less warfarin to achieve the same level of anticoagulation as compared to those with 'group B' haplotypes (71). The mean doses of warfarin for those with group A/A, A/B and B/B haplotypes were 2.7 mg/day, 4.9 mg/day and 6.2 mg/day, respectively (71). In addition, this study found that African-Americans were more likely to have group B haplotypes and Asian-Amerians were more likely to have group A haplotypes (71).

As a result of these findings and other studies that have suggested that up to 60% of an individual's dose-response to warfarin can be explained purely on the basis of known genetic polymorphisms (16, 70, 71), many studies have sought to determine if initiating Warfarin dosing according to the results of genetic testing (so-called pharmacogenetic-guided therapy (PGT)) is beneficial in terms of clinical outcomes (13, 72-77). To date, no large RCTs have demonstrated a significant benefit in terms of clinical outcomes and pharmacogenetic dosing of warfarin is currently not recommended per the 2012 ACCP guidelines (2). Given the costs of routine genotyping, there is some evidence to suggest

that, even if pharmacogenetic dosing is ultimately shown to have a meaningful clinical benefit, it is unlikely to be cost-effective: one study that considered pharmacogenetic information for warfarin dosing reported that for typical patients with atrial fibrillation the marginal cost-effectiveness of the testing was over US$170,000 per quality-adjusted life-year gained (78).

Drug Interactions

At least 120 different medications have been reported to interact with warfarin and this list is progressively increasing (3, 27). It should be noted that the quality of evidence supporting particular drug interactions with warfarin is frequently limited (3). Nonetheless there are several mechanisms by which drug interactions with warfarin have been well documented (79). Medications that interfere with Vitamin K metabolism either directly (or by altering the amount of bacterial Vitamin K synthesis in the gut (e.g. antibiotics)) can have a variable effect on the response to warfarin (79). Other medications have been shown to directly interfere with warfarin metabolism (79). In addition, drugs that don't interfere with Vitamin K or Warfarin metabolism may otherwise predispose patients on warfarin to an increased risk of bleeding or thrombosis: for example, anti-platelet agents that themselves have anticoagulant properties may be independently (or synergistically) associated with gastrointestinal or other bleeding events (79).

Dietary Vitamin K

Ongoing variations in dietary Vitamin K intake profoundly affect the level of anticoagulation achieved with maintenance warfarin therapy (80-86). In addition to

traditional dietary sources of Vitamin K (green leafy vegetables), multivitamins, herbal products and other dietary supplements containing Vitamin K can also affect the degree to which warfarin results in therapeutic anticoagulation (87, 88).

Smoking

A systematic review and meta-analysis by Nathisuwan *et al*. (2011) (89) included 12 cross-sectional studies and one experimental pharmacokinetic study. The authors' meta-analysis included 2133 subjects (from the four cross-sectional studies for which it was possible to adjust for pharmacogenetic factors (90-93)) and concluded that smoking was associated with a 13.21% (95% CI, 8.59%-17.83%; $P < .001$) increase in the warfarin dosage required relative to nonsmokers (89).

2.1.5 Complications Associated with Warfarin

2.1.5.1 Bleeding

Warfarin is widely used as a poison for rats and mice: it kills rodents after they ingest it by inducing such profound anticoagulation that they consequently spontaneously bleed to death. Warfarin was initially created for this purpose in the 1940s (94) and was approved for commercial use as a 'rodenticide' in 1948 prior to its approval for clinical use as an anticoagulant medication for humans in 1954 (94). With this in mind, it is not surprising that bleeding is the most important potential complication of medical therapy with warfarin.

While the specific clinical indications for anticoagulation with warfarin are detailed in the section above, more generally, the use of anticoagulant therapy is predicated on the

assumption that it will decrease the risk of developing (or treat existing) thrombotic conditions without resulting in a comparable increase in the risk of bleeding. Nonetheless, as previously discussed, in order to be effective at preventing thrombosis, all therapeutic anticoagulants increase the risk of bleeding to some degree and their usage involves balancing the risks related to thrombosis with the bleeding risks of anticoagulation therapy.

Warfarin is recognized as a 'narrow therapeutic index drug' (95) meaning that precise (and individualized) dosing is required to maintain the level of anticoagulation induced in the therapeutic range (i.e. enough to prevent or treat thrombosis but not so much as to significantly increase the risk of bleeding).

There is much evidence that bleeding complications associated with warfarin cause significant morbidity and mortality:

- Warfarin was found to be one of the drugs (along with Insulin) most commonly associated with adverse events (in this case, bleeding) based on United States (US) emergency department (ER) data in 2002 (96) and also when the same data was reviewed for 2004 to 2005 (97). Major bleeding (defined as retroperitoneal, intracranial, resulting in transfusion, hospitalization or directly to death) was estimated to occur in up to 10% (98) to 16% (99) of patients treated with warfarin. This does not compare favourably with the incidence of serious adverse events for most approved drugs, typically being less than 1 in 1000 (100).
- A review of randomized controlled trials (RCTs) by Landefeld *et al*. (1993)

(101) reported that in patients treated with warfarin for a variety of indications (n = 3931) (i.e. atrial fibrillation, coronary artery disease, cerebrovascular disease and following hip surgery), bleeding events occurred in 14% compared to 3% for patients with the same indications but not treated with an anticoagulant (i.e. control arms) (n = 3583). The relative risk (RR) (95% Confidence Interval (CI)) for death secondary to bleeding was 4.8 (2.1 – 10.8).

- A 2007 study by Wysowski *et al*. (100) took a multipronged approach to assess the frequency and importance of bleeding complications due to warfarin. The authors accessed the 'National Prescription Audit *Plus'* database to project the number of outpatient prescriptions dispensed by all retail pharmacies in the US (including those from drugstore chains, mail order, food stores and long-term care facilities). They also extracted data from the US Food and Drug Administration (FDA) Adverse Events Reporting System (AERS). The AERS database, which consists of voluntary reports of adverse events suspected to be related to prescription drug use, was used to determine the number of reports of fatal and serious bleeding outcomes suspected to be due to warfarin from 1993 through to July 2006. The 'serious bleeding outcomes' included hospitalization for bleeding, 'life-threatening' bleeding, disability, and bleeding for which intervention was required (100). The AERS database was also used to rank the serious adverse events specifically reported for warfarin. Another source of information this study used was registry data from the US Division of Vital Statistics of the National Center for Health Statistics (NCHS). Specifically, NCHS data was used to determine the number of deaths in which

'anticoagulants' were listed as either the immediate, contributing or underlying cause of death (or as a "significant condition leading to death") (100). A final source of data was the National Hospital Ambulatory Care Survey (NHAMCS), a probabilistic sample survey of US ERs. This was used to estimate the number of ER visits associated with warfarin as well as the number of visits in which warfarin was mentioned (i.e. visits in which warfarin was listed as a medication that was prescribed, supplied, administered or currently used) and there was a concurrent diagnosis of bleeding (according to *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) codes linked to those visits). The results were impressive, not only in terms of the increase in the estimated number of dispensed warfarin prescriptions in the US---which climbed from 21,095,000 in 1998 to 30,632,000 in 2004 (100)---but also in terms of bleeding complications. Warfarin ranked ninth overall, amongst all medications for which adverse reports existed in the AERS database for the years between 2000 and mid-2006, with over 4500 reports (100). In 2003 and 2004, anticoagulants in general were mentioned more than any other drug class with respect to 'adverse events during therapeutic use' on US death certificates. This reflects there having been 1482 total 'mentions' of anticoagulants on death certificates in 2003 with 46 cases in which anticoagulants were listed as the underlying cause of death (100). In 2004, the corresponding numbers were 1521 death certificates in which anticoagulants were mentioned and 46 in which they were classified as being the underlying cause of death (100). The NHAMCS data also pointed to a significant burden of ER visits due to bleeding

complications related to warfarin: more than 29,000 ER visits for bleeding complications per year. Overall, the authors concluded that their results were consistent with those of the abovementioned RCTs (98, 99) that had reported major bleeding for up to 10 to 16% of warfarin users over shorter periods of follow-up.

- As a result of the work by Wysowski *et al*. (100), as detailed above, the high frequency of bleeding complications due to warfarin treatment was recognized by the US FDA such that a "black box" warning about warfarin's bleeding risk became mandatory for US product labeling as of 2006 (100). The "black box" warning is used to convey information about warfarin's increased bleeding risk to physicians (102). In addition, a medication guide is now required to be provided to patients with each warfarin prescription in the US (103). This guide (103), and other similar commonly used (100) educational literature for patients (104), educates patients that they should immediately inform their healthcare provider if they begin to experience any bleeding symptoms while on warfarin (103, 104). In Canada, the responsible regulatory agency, the Health Protection Branch (HPB) of Health Canada, does not issue a specific warning for the bleeding risk however the manufacturer of all warfarin available for medical use in Canada carriers the same warnings as the FDA-stipulated "black-box" warnings used in the US in the product monograph. Distribution of a patient medication guide is not mandatory with warfarin prescriptions in Canada.

Given that the increased risks of bleeding with warfarin therapy have been well documented and can be viewed as an unfortunate extension of its therapeutic effect, many

studies have been undertaken in an effort to identify patients at the highest risk of bleeding with anticoagulation therapy using warfarin (or other VKAs). Significantly increased risks of bleeding have been found for particular patient subgroups (as detailed below).

2.1.5.2 Risk Factors for Bleeding

The following patient characteristics are associated with an increased risk of bleeding following the use of VKAs:

- **Presence of advanced kidney disease or elevated serum creatinine (a marker of kidney dysfunction)**

  For their 2009 paper entitled "Kidney Function Influences Warfarin Responsiveness and Hemorrhagic Complications", Limdi *et al*. conducted a secondary analysis of a prospective cohort study that included 578 patients on Warfarin (105). The prospective cohort study, called POAT (Pharmacogenetic Optimization of Anticoagulation Therapy), enrolled patients on anticoagulation with a target INR of 2 to 3 (106) and aimed to assess the role of genetic variations in warfarin dosing requirements. The secondary analysis assessed the relationship between kidney function and anticoagulation control, warfarin dosage, and the risk of bleeding (105). Kidney function, in terms of the degree of chronic kidney disease (CKD) present, was defined according to the estimated glomerular filtration rate (eGFR) as 'minimal/none', 'moderate' and 'severe' using cutoffs of $\geq$60 ml/min per 1.73 m^2, 30 to 59 ml/min per 1.73 m^2 and <30 ml/min per 1.73 m^2, respectively (105). The cutoffs used to define 'moderate' and 'severe' CKD

accord with the Kidney Disease Outcomes Quality Initiative (KDOQI) classification scheme for CKD as stage 3 CKD and stage 4 CKD (107). It should be noted that 47 of the 53 patients with 'severe' CKD had end-stage-renal-disease (ESRD) and were on dialysis (stage 5 CKD) (105). After multivariate adjustment for clinical and genetic factors, patients with 'severe' CKD were found to have significantly lower warfarin dosage requirements and significantly poorer anticoagulation control (i.e. time with INR in the target range) compared to those with 'minimal/none' and 'moderate' CKD (105). In addition, those with 'severe' CKD were found to have a significantly increased risk of major bleeding with a hazard ratio of 2.4 (95% CI 1.1 – 5.3) relative to those with 'minimal/none' and 'moderate' CKD (105). These results suggested that, in patients with more advanced CKD, warfarin treatment should be initiated and maintained at lower doses than for patients without CKD (106).

A subsequent cross-sectional study by the same group then sought to assess the degree of Warfarin dose reduction associated with 'moderate' or 'severe' CKD (108). Data from the POAT cohort was combined with data from a similar cohort study, GEDWR (Genetic and Environmental Determinants of Warfarin), that was, like POAT, designed to define the influence of genetic variations on warfarin dosing and also enrolled patients being managed by an anticoagulation clinic who had a target INR of 2 to 3 (n = 708) (108). In addition, 272 patients managed at the anticoagulation clinic at another centre were included for study, for a total enrollment of 980 patients. Similar results were found overall and for the individual cohorts studied: warfarin doses were significantly lower for those with

'moderate' and 'severe' CKD (as defined above) compared with those with 'minimal/no' CKD. Overall, patients with 'moderate' CKD required 9.5% lower doses of warfarin, and those with 'severe' CKD 19% lower doses of warfarin, compared with those who had 'minimal/no' CKD (108).

In 2013, the same group reported the results of an analysis of POAT and GEDWR data that was undertaken to assess whether the risk of hemorrhage differed for patients on warfarin depending on their severity of kidney disease. When classifying kidney disease, they distinguished between whether patients with stage 3 CKD had either stage 3a or 3b as there has been some suggestion that stage 3 CKD which includes all those with an eGFR 30-59 ml/min per 1.73 m^2 provides too broad a categorization and fails to capture important differences between groups of patients with eGFRs at opposite ends within the specified range (109). As such, Stage 3a is defined as eGFR 45-69 ml/min per 1.73 m^2 and Stage 3b as eGFR 30-44 ml/min per 1.73 m^2 (110). This analysis included 1245 patients and over a two-year period of follow-up assessed the occurrence of major hemorrhagic events (109). The authors did not specify the number of patients with ESRD on HD however there were 113 patients included who had an eGFR < 30 ml/min per 1.73 m^2. Over the period of follow-up, 127 major bleeding events were recorded. Across the spectrum, lower eGFR was associated with an increased risk of major bleeding: relative to those with an eGFR ≥ 60 ml/min per 1.73 m^2, patients with an eGFR of 30-44 ml/min per 1.73 m^2 and less than 30 ml/min per 1.73 m^2 had RRs of 2.11 (95% CI 1.01-4.41) and 5.65 (RR 3.11-10.27), respectively (109).

Overall, it can be concluded that moderate to severe kidney dysfunction is associated with needing lower doses of warfarin, worse anticoagulation control and, most importantly, an increased risk of major bleeding. It should be noted that because the above-mentioned studies did not consider thrombotic events and, as a result, no conclusions relating to the overall risks and benefits of anticoagulation therapy can be made on the basis of these studies. It should be noted that there is evidence that patients with CKD and ESRD are at elevated risk of thrombotic events (111-115) such as cerebrovascular accidents (CVAs) related to atrial fibrillation. While this section has focused on the relationship between increased bleeding risks with warfarin for patients with CKD (encompassing studies which did include some patients with ESRD on HD), studies that have focused specifically on the risks and benefits of anticoagulation for patients with ESRD on HD (54, 116-121) are discussed in more detail below.

Other patient characteristics shown on one or more multivariate analysis to be associated with a significantly increased risk of bleeding include:

- **Increasing age** (122-130) sometimes specifically defined as age ≥ 65 years (122, 130) or age ≥ 75 years (123, 124, 127, 128, 131).
- Concurrent use of certain other medications including **other antithrombotic drugs** (anti-platelet agents such as acetylsalicylic acid (ASA) and clopidogrel) (123, 132-136) and commonly used **cholesterol-lowering drugs** (i.e. fibrates and statins)) (137).
- Poorly controlled hypertension (131)

- Diabetes mellitus (DM) (122, 123)
- Anemia (122, 127, 128, 130)
- Poor drug compliance or clinic attendance (131)
- Presence of malignancy (126-128)
- Alcoholism / liver disease (124, 138)
- Female sex (126)

Factors related to INR control and associated with an increased risk of bleeding with warfarin include:

- Instability of INR control and INR > 3 (131, 139)
- Pre-treatment INR > 1.2 (125)
- Previous severe hemorrhage while being treated with warfarin while having an 'in-range' INR (128, 131)

Poor anticoagulation control (i.e. maintaining the INR in the target range) is thought to be an important factor in determining the occurrence of adverse events related to warfarin use: over-anticoagulation (i.e. INR above the therapeutic range) predisposes to bleeding however under-anticoagulation (i.e. INR below the therapeutic range) increases the risks of thrombotic events related to the indication for which warfarin has been prescribed. Support for this concept comes from a meta-analysis of 45 studies that assessed the risks of bleeding and thromboembolism while on warfarin treatment (140). This study included a total of 71,065 subjects (140). Overall, 44% (95% CI: 39-49%) of hemmorhagic events occurred when the INR was above the therapeutic range and 48% (95% CI: 41-55%) of thromboembolic events took place when the INR was below the therapeutic range (140).

This suggests that there is significant room for improvement in anticoagulation control for patients taking warfarin and that improved anticoagulation control is likely to reduce the frequency of adverse events in this population (140).

2.1.5.3 Bleeding-Risk Scoring Systems:

Multiple retrospective and prospective observational studies have derived scoring systems in an attempt to estimate the bleeding risk for individuals started on warfarin (44, 122, 124, 126, 128, 130, 141). Nonetheless, systematic reviews of studies assessing the predictive performance of commonly used scoring systems (142, 143) (including assessments of the Outpatient Bleeding Risk Index (OBRI) and the modified OBRI (mOBRI), 'HAS-BLED' bleeding risk score, ATRIA risk score and HEMORR2HAGES risk index) concluded that none has "sufficient predictive accuracy or [has] had sufficient validation to be recommended for routine use in practice" (143).

2.1.5.4 Complications of Warfarin Other Than Bleeding:

While bleeding is by far the most commonly reported serious complication of warfarin therapy, several other important complications have been recognized to be directly attributable to the medical use of Warfarin:

- **Cardiovascular calcification**

  One of the hepatic effects of VKAs is to inhibit the synthesis of proteins shown to be involved in the inhibition of vascular calcification (144). The use of VKAs has been shown to be associated with significantly increased prevalence and significantly increased severity of aortic valve and coronary

artery calcification (145-147). One study of HD patients demonstrated that aortic valve calcification was significantly worse amongst those who had a history of long-term warfarin use (145).

- **Calcific uremic arteriolopathy (CUA)** (also called 'calciphylaxis')
  CUA is a condition characterized by microvascular calcification and thrombosis resulting in skin necrosis (148). This condition is most commonly seen in patients with ESRD and consequent hyperparathyroidism (148). Treatment with warfarin has also been described to be a risk factor for the development of CUA: approximately half of the 180 patients in a German registry of CUA patients developed the condition soon after having started treatment with a VKA (149). As well, a case-control study of patients on dialysis in Japan showed that treatment with a VKA was associated with significantly increased odds of developing CUA (OR 11.4, 95% CI 2.7-48.1, P=0.0009) (150).

2.1.6 Warfarin Anticoagulation in Hemodialysis Patients

Warfarin Anticoagulation for the Prevention and Treatment of Deep Vein Thrombosis and Pulmonary Embolism in Hemodialysis Patients:

In HD patients, warfarin is the clear first choice oral anticoagulant for indications in which the risk of thromboembolism without treatment using warfarin significantly outweighs the risk of complications such as bleeding (i.e. mechanical heart valves, VTE, APAS) (144). Notably, HD patients are at increased risks of having VTE:

- The incidence of death secondary to pulmonary embolism in a cohort of over 130,000 incident HD patients (from the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) registry) was found to increased relative to the general population (151). The mortality rate ratio (death due to pulmonary embolus) was 12.2 for HD patients compared to the general population after being adjusted for age and sex (151).
- Similarly, the incidence of DVT has been reported to be 5.6 times greater for HD patients than for healthy controls (152).

Warfarin Anticoagulation for the Prevention of Cerebrovascular Accidents in Hemodialysis Patients:

Atrial fibrillation is common for patients on HD with a prevalence of between 11% and 27% (153-155) which has been shown to be increasing (156).

For the indication of atrial fibrillation, the risks and benefits of warfarin anticoagulation are less clearly defined in the HD population. There are multiple reasons why patients with ESRD on HD might have a different risk-benefit profile for warfarin anticoagulation than that of the general population:

- In addition to having uremic platelet dysfunction, HD patients may have a "background of small vessel disease and mucousal inflammation [that] increases the risk of clinically important major bleeding episodes" (157). The thromboembolic disease associated with both CKD and atrial fibrillation is promoted by hypercoagulability, abnormal blood flow (stasis) and predisposing

endothelial damage. As such, CKD and atrial fibrillation may synergistically increase the risk of thrombotic complications including CVA (115, 154). In a Danish study of over 130,000 patients with atrial fibrillation, those on HD had an 83% higher rate of CVA relative to those with no history of kidney disease (114).

- A Canadian study illustrated that subclinical Vitamin K deficiency, a known risk factor for bleeding with warfarin therapy, is common in HD patients (158).
- Many patients receive heparin during HD to prevent access complications. Theoretically, there may be an increased risk of bleeding due to the use of more than one anticoagulant simultaneously. As well, monitoring of INR in this context may also be more complicated: one study found that the strongest independent predictor of a falsely elevated INR test result is that the patient was undergoing HD treatment at the time of testing (159).
- As described above, HD patients are at increased risk of CUA when receiving warfarin anticoagulation. In addition, increased aortic calcification has been specifically demonstrated in the HD population (145).
- Since HD patients typically receive HD treatments three times per week in a clinical setting with easy access to blood testing, it is most likely that HD patients on anticoagulation have their anticoagulant dosing managed by the medical personnel of the HD clinic/unit (as opposed to management by a family doctor or specialized anticoagulation clinic). More frequent contact with the patient in the context of regular HD treatments might influence the degree of INR-control by improving compliance (131).

The use of warfarin anticoagulation in the HD population has been a focus of study in recent years:

- In 2007, a systematic review that included 7 observational studies of full-intensity warfarin anticoagulation as well as a single RCT of low-intensity anticoagulation in the HD population, showed that the rate of major bleeding episodes was approximately twice as high as that for HD patients who were not receiving oral anticoagulation (or were receiving subcutaneous low-molecular-weight heparin) (118). At that time, the recommendation by experts in the field was that "providers should consider standard warfarin anticoagulation in HD patients with chronic atrial fibrillation, adhering to screening and monitoring as in the general population" (160).
- Other observational studies of warfarin use for atrial fibrillation in HD patients have had conflicting results. In a U.S. study of 1671 incident HD patients with a preceding diagnosis of atrial fibrillation, the use of warfarin was associated with almost double the risk of a subsequent CVA (HR 1.93; 95% CI: 1.29 to 2.90) however was not associated with a relative increase in all-cause mortality (161). It should be noted that CVAs in this study included both thrombotic and hemorrhagic CVAs (161).

  An analysis of data from the international Dialysis Outcomes and Practice Patterns Study (DOPPS) showed that of 17,513 randomly sampled HD patients, 2188 had preexisting atrial fibrillation (115). Amongst those with atrial fibrillation, the use of Warfarin was found to be associated with an increased risk of CVA or death for those over 75 years of age only (115).

Another analysis of DOPPS data included 48,144 HD patients from 12 countries and sought to define factors predictive of bleeding and CVA (162). The authors reported that the rates of overall mortality, cardiovascular mortality and bleeding (defined as that which required hospitalization) were increased for patients on oral anticoagulation across adjusted models (162). Those patients who had an episode of gastrointestinal bleeding recorded in the preceding year were found to be at very high risk of a major bleeding event: for those patients, the bleeding rate was more than twice the rate of CVA across all CHADS2 scores (162). This study also demonstrated that, for HD patients with atrial fibrillation---a group that was excluded from the studies which established the CHADS2 scoring system (163)---CHADS2 scores were predictive of the future risk of CVA (162).

One study of prevalent HD patients who then developed atrial fibrillation compared 237 warfarin users with 948 propensity-score matched non-warfarin-using controls (164). There was no difference in the risk of ischemic CVA (HR 0.92; 95% CI, 0.61-1.37) between groups however there was an increased risk of hemorrhagic CVA associated with warfarin use (HR 2.38; 95% CI, 1.15-4.96) (164). No significant difference in the frequency of gastrointestinal bleeding or overall mortality was observed between the groups (164).

The previously mentioned Danish registry study included 901 prevalent ESRD patients and found that their rate of CVA or VTE was increased relative to those without kidney disease (HR, 1.83; 95% CI, 1.57 to 2.14; $P<0.001$) however warfarin use was associated with a 56% reduction in risk (114). The generalizability of this study to the North American HD population may be

somewhat limited as there was a low burden of comorbid illness amongst the included HD patients in this study (114).

A recent Swedish registry study of survivors of myocardial infarction with atrial fibrillation showed that for the 408 patients included with ESRD, warfarin use was associated with a 43% (95% CI, 14-63%) decrease in the risk of subsequent ischemic CVA, myocardial infarction or death (165). Conversely, an increased risk of bleeding was not associated with warfarin use (HR 0.52; 95% CI, 0.16-1.65) (165).

Another recent study of patients admitted to hospital in Quebec and Ontario with a diagnosis of AF included 1626 patients on HD or peritoneal dialysis (and also examined data from 204,210 non-dialysis patients) (166). This study examined the association between subsequent use of warfarin and the risk of CVA and bleeding events in both the dialysis and non-dialysis populations. Non-dialysis patients were found to have a slight reduction in CVA risk (defined as any ischemic CVA and including transient ischemic attacks (TIAs) and retinal infarction) with warfarin use (HR 0.87, 95% CI, 0.85-0.90). They were also found to have a modestly increased risk of a bleeding event (defined to include intracerebral bleeding, GI bleeding, intraocular bleeding, hematuria or other bleeding) with Warfarin use (HR 1.19, 95% CI, 1.16-1.22). For the dialysis patients, warfarin use was not associated with a significantly lower risk of CVA (HR 1.14, 95% CI, 0.78-1.67) however it was associated with a significantly increased risk of bleeding (HR 1.44, 95% CI, 1.13-1.85). It is notable that the likelihood of being placed on warfarin after an admission for atrial fibrillation was

not significantly different for dialysis patients compared to non-dialysis patients (166).

- For all of the abovementioned observational studies assessing the risks of warfarin in HD patients, it must be recognized that there are potential biases related to unmeasured or residual confounding, particularly confounding-by-indication: those determined to be at the highest risk of a poor outcome may also be more likely to be selected to receive therapy (e.g. those at highest risk of CVA are more likely to be put on treatment with warfarin).

Based on the conflicting results of the abovementioned large observational studies, in the absence of evidence from RCTs, it remains unclear which HD patients with AF should be treated with warfarin (167).

2.2 Outpatient Management of Warfarin Anticoagulation

Given the multiple (and dynamic) factors that affect individual patients' responses to warfarin therapy, ongoing monitoring and dose adjustment is required. This is particularly important given the evidence that, in an otherwise unselected population, when warfarin treatment is indicated for AF, overanticoagulation (INR > 3) is associated with an increased risk of bleeding while underanticoagulation (INR < 2) is associated with an increased risk of CVA (168-170).

2.2.1 Computerized Clinical Decision Support Systems

A computerized clinical decision support system (CDSS) applies a proprietary software algorithm to a database that contains patient-specific data in order to generate a clinical recommendation (171). CDSSs have been used in a variety of clinical settings including that of helping to guide the dosing of systemic oral anticoagulants such as warfarin. A CDSS, used for this purpose, applies an algorithm to a database that contains a record of the previously prescribed doses of anticoagulant and INR results for a particular patient. The algorithm returns a dosage recommendation targeted to achieve (or maintain) the patient's INR within a specified therapeutic range. It also provides a recommendation as to when repeat testing of the INR should be performed.

2.2.2 Computerized Decision Support Systems for Outpatient Management of Warfarin Anticoagulation

There are several different proprietary algorithms that have been studied for anticoagulation control with the 'DAWN AC' system being the most studied to date (172).

The use of a CDSS to guide oral anticoagulant dosing has been shown to be effective in improving anticoagulation control compared with traditional 'manual' drug dosing guided by medical personnel only (138, 173-176). Many studies have demonstrated a significant improvement when the surrogate laboratory parameter of "time in target INR range" (TIR) has been used as the primary outcome (138, 173-175, 177). There is evidence that an increased TIR is associated with a reduced number of adverse events due

to over or under-anticoagulation (140, 178). Studies of 'usual care' have generally shown TIR to be < 50%, whereas CDSSs typically attain TIR of 65% or higher, a range shown to be associated with significantly reduced complications (140, 172, 178). Even stronger evidence for the safety and efficacy of using a CDSS to guide anticoagulant dosing comes from the European Action on Anticoagulation (EAA) study. The EAA was a multicentre RCT which enrolled 13,209 patients to compare the use of a CDSS for warfarin-dosing with traditional, 'medical-personnel' guided dosing (176). The use of the CDSS resulted in an improved TIR with near-identical outcomes with respect to clinical events such as bleeding and thrombosis when compared with usual care. A substudy of EAA that involved patients after five years of follow-up (n=2631) also showed that adverse clinical events were nearly identical for those managed with CDSS compared with manual dosing (176).

On the basis of the aforementioned studies, there is good evidence to support the implementation of CDSSs to guide anticoagulant dosing for non-selected outpatients. As well, a cost-effectiveness analysis reported in conjunction with the EAA reported reduced costs of using the CDSS to manage anticoagulation compared with manual dosing (75). Given that it is, at a minimum, equally clinically efficacious compared with manual-dosing, the conclusion was that "investment in this technology represents value for money" (75).

The aforementioned studies have generally been conducted in otherwise-unselected patients referred for anticoagulation follow-up, usually through a specialized clinic.

Although HD patients were not specifically excluded from any of the previous studies of CDSSs that were cited above, we are not aware of any studies that have described the use of a CDSS to guide oral anticoagulant dosing in the HD population.

One study of 67 HD patients did compare the use of a nurse-led electronic nomogram to routine physician-led management of warfarin dosing and INR testing (179). Unlike a CDSS, an electronic nomogram does not utilize a patient-specific database of past INR results to produce dosing and INR testing recommendations. The authors reported that INR control did not differ significantly pre- and post- implementation of the electronic nomogram however there was a significant decrease in the frequency of INR testing following implementation of the nomogram (179). This is the only previous study to assess the use of any type of decision-support for Warfarin dosing specifically for HD patients.

2.3 Summary of Background and Literature Review

Warfarin is an oral anticoagulant with complex pharmacologic characteristics (refer to sections 2.1.1 to 2.1.4). Given the risks of over- or under-anticoagulation, the use of warfarin necessitates careful dose-adjustment and monitoring (refer to sections 2.1.2 and 2.1.5). In particular, the use of warfarin in the HD population may be more likely to be associated with bleeding or thrombotic complications than it is for the general population (refer to section 2.1.6). CDSSs have been shown to be effective tools to assist in the management of warfarin dosing and INR testing (see section 2.2). Given that the HD population may have a different risk-benefit profile, it was possible that the use of a

CDSS for HD patients could result in more or less effective anticoagulation control than had been observed in non-HD patients. On this basis, a study to examine the impact of CDSS-guided warfarin management specifically for HD patients was justified.

3.0 METHODS:

Given the well-documented safety, efficacy and cost-effectiveness of the 'DAWN AC' system (see section 2.2.2), the Division of Hematology at The Ottawa Hospital (TOH) implemented its use for the management of patients referred to the thrombosis clinic for management of warfarin anticoagulation. A study documenting its successful usage at the TOH, as well as the implementation of an automated voice response system to notify patients of any dosing changes was published in 2009 (177).

The Division of Hematology, in conjunction with the Division of Nephrology, made an administrative decision to expand the use of the 'DAWN AC' system to manage HD patients' anticoagulation at all of the TOH HD units as well as the satellite HD units starting in June 2011. This study sought to capitalize upon the implementation of the 'DAWN AC' system in the HD units in order to better characterize anticoagulation control in HD patients generally and, more specifically, determine how the implementation of a CDSS impacted upon anticoagulation-control in this special population.

3.1 Study Design

The study was a quasi-experimental, before - after study with prospective and retrospective data-collection.

3.2 Study Objectives

3.2.1 Primary Objective

To determine if the implementation of a CDSS to manage systemic warfarin anticoagulation in HD patients is associated with anticoagulation control that is superior to that which is achieved with usual, 'medical-personnel directed' management.

3.2.2 Secondary Objectives

1) To compare the frequency with which laboratory testing of the INR is undertaken before and after implementation of a CDSS for HD patients.
2) To characterize systemic anticoagulation control in the HD population compared with what has been reported for otherwise-unselected patient groups.
3) To compare the occurrence of adverse events related to poor anticoagulation control before and after implementation. (A formal safety analysis was not undertaken due to the likelihood of insufficient statistical power).

3.3 The Intervention

The intervention was the implementation of a pharmacist-managed CDSS (DawnAC, 4S Information Systems Ltd., Milnthorpe, England) to assist in guiding HD patients' Warfarin dosing and INR monitoring.

'Usual care' was adjustment of warfarin dosing and INR testing according to the prior existing strategy: directed by the nephrologist(s) covering the HD-units of patients taking warfarin. Typically nephrologists performed adjustments at times when a patient's INR

result was reported to them by nursing staff or at the time of reviewing routinely ordered HD monthly blood work that typically included INR testing for those patients on warfarin.

For CDSS-based management (the intervention), suggestions of the CDSS regarding changes in Warfarin dose and/or timing of next INR testing were relayed by the pharmacist responsible for operating the CDSS to the HD-unit where the patient was receiving dialysis and via telephone contact with the patient in order to be implemented directly without physician involvement. The pharmacist could alter the recommendation of the CDSS in special circumstances only (e.g. if the CDSS was unable to make a recommendation). These pharmacists' work is supervised and conducted on behalf of thrombosis specialist physicians within the Division of Hematology.

3.4 Data Collection

For individual patients, any INR data from the 3 months prior to them having their anticoagulation management switched from 'usual care' to the CDSS was collected from the OACIS database. In addition, a retrospective chart review (including OACIS and *NephroCare* database review) was conducted to obtain baseline demographic and other baseline information. From the date following implementation of CDSS management of their anticoagulation, 9 months of INR data was collected. Throughout the follow-up period, the *NephroCare* and OACIS database was reviewed on a monthly basis to determine if adverse events, as defined below, had occurred and additional information was obtained from the dialysis unit staff if necessary.

Case report forms can be found in Appendix A.

3.5 Study Timeline

- December 1st, 2010 – Study Initiation
    - Final REB approval obtained
    - Case report forms created and database established
- May 5th, 2011 - Data collection began
- June 18th, 2014 - Data collection finished
- May 1st 2014 – August 20th, 2014
    - Database 'clean up', verification and correction of data queries and performance of data analysis

3.6 Recruitment

- All eligible patients were identified by monthly screening for active prescriptions for warfarin entered in the *NephroCare* database (which keeps up-to-date records on medications for all TOH HD patients, including home dialysis and satellite units, of TOH). The study received approval from the Ottawa Hospital Research Ethics Board (OHREB) to be undertaken with waived consent (see Appendix B for OHREB documentation).

3.7 Inclusion Criteria

- 18 years of age or older
- Prevalent or incident chronic hemodialysis patients receiving regular HD at one of the TOH hospitals, satellite HD units or through the home-dialysis program.
- Receiving a prescription for warfarin (for any indication)
- Stable anticoagulation control. Patients were deemed to have stable anticoagulation control if they have been taking warfarin for more than two weeks and had three consecutive INR measurements in the therapeutic range.

3.8 Exclusion Criteria

- Receiving oral anticoagulation other than warfarin
- Warfarin dosing managed by a physician other than the nephrologist(s) covering their HD unit.
- INR testing data not available from both pre- and post-intervention periods (i.e. before and after initiation of the CDSS).

3.9 Outcome Measures

3.9.1 Primary Outcome Measure

- Time in Range (TIR):
    - A multi-step method was used to determine the TIR. As described by Rosendaal *et al*. (180), linear interpolation was used to calculate the INR values for the days between actual measurements. For each patient, the proportion of days, during the specified

observation period, in which the INR was within the therapeutic range, was calculated. This value, multiplied by 100%, resulted in the TIR (180).

3.9.2 Secondary Outcome Measures

- Frequency of INR testing:
    - The number of times an INR test was conducted during the specified observation period divided by the number of days in that observation period.
- Major bleeding was defined by the International Society of Thrombosis and Hemostasis (181): overt bleeding with at least one of the following criteria:
    - Associated with a fall in hemoglobin of 20 g/L or more, or;
    - Leading to a transfusion of 2 or more units of packed red blood cells or whole blood, or;
    - Occurring in a critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal, or;
    - Contributing to death
- Venous thromboembolic (VTE) events:
    - Clinical or radiologic diagnosis of deep vein thrombosis (DVT)
    - Clinical or radiologic diagnosis of pulmonary embolus (PE)
- Cerebrovascular events:
    - Clinical diagnosis of a Transient Ischemic Attack (TIA)

    - Clinical diagnosis of a Reversible Ischemic Neurologic Deficit (RIND)
    - Clinical or radiologic diagnosis of a Cerebrovascular Accident (CVA)
- Unexpected death attributed to VTE, major bleeding or CVA.

3.10 Data Analysis

The TIR for the 2 study periods (pre- and post-intervention) was compared using a Wilcoxon signed-rank test for paired samples assuming a two-sided alpha of 0.05. A Wilcoxon signed-rank test was also used to compare the pre- and post-intervention frequency of INR testing. The reasons for choosing to use this non-parametric test were:

- TIR (the primary outcome measure) is a proportion and is therefore not a continuous variable that can be normally distributed.
- TIRs (pre- and post-implementation) were not anticipated to have a near-normal distribution within the confines of the TIR range of 0 to 100%.

Subgroup analyses were not performed due to the small numbers of patients within subgroups (such as 'according to target INR' or indication for anticoagulation).
Given that there was a possibility that a Hawthorne effect could occur in the immediate post-intervention phase or that there might be initial difficulties with implementation that could negatively affect the primary outcome of TIR, the initial 14 days post-implementation was censored from observation. Time periods during which patients were admitted to hospital were censored from observation in addition to 14 days following

hospitalizations (not including emergency department visits). Time periods where warfarin was temporarily held in anticipation of a procedure were censored from observation in addition to 14 days following resumption of warfarin.

In addition to performing a paired comparison of anticoagulation parameters during the pre- and post-intervention periods for all included patients (as described above), adverse events were tracked and reported for all patients who were initially included in the study but were later excluded for not having data available from the post-intervention period (i.e. due to death or discontinuation of warfarin prior to the intervention).

3.11 Sample Size Calculation

Since the primary outcome of difference in TIR (pre- versus post-intervention) was assessed using a non-parametric test for paired samples (the Wilcoxon signed-rank test), it was necessary to perform a sample-size calculation assuming that the primary statistical analysis would be conducted using a paired t-test for mean difference.

With respect to the primary outcome, the number of subjects (with each subject providing a pre- and post-intervention TIR) required to have ≥ 80% power to detect a 10% difference in mean TIR with 95% confidence was determined to be 41 (which would yield an actual power of 80.5% to detect a 10% difference). Dropout due to death, change of dialysis modality or renal transplantation over the time period of the study was not anticipated to be a major issue given the duration of data collection required (see below). The primary sample size calculation was based upon the following:

- The effect size of an absolute 10% change in TIR was based on the minimum change likely to be clinically significant. Previous studies showed physician-managed TIR to be approximately 50% and TIR using a CDSS approximately 65% or more (138). Studies had also shown that there was no appreciable difference in clinical outcomes (death, major bleeding, VTEs) in the context of absolute TIR increases of approximately 5%. As such, we chose to detect a 10% relative change in TIR for the purposes of the sample size calculation: assuming a relative 10% increase (or decrease) in a TIR of 50% is equivalent to an absolute increase (or decrease) of 5%.
- The standard deviations of TIR estimates for both the pre- and post-intervention TIRs (used in the sample size calculation) were derived directly from the largest study to date that used the DAWN AC system (176): 17.7% for pre-intervention TIRs and 16.4% for post-intervention TIRs. This made for a pooled sigma (standard deviation) of 0.17 used for the sample size calculation.
- In order to further err on the side of making a conservative estimate for the required sample size, it was assumed there would be a weak correlation between pre- and post-intervention TIRs of 0.15 for individual patients. Assuming a moderate correlation (0.5) and all else unchanged would have led to a sample size estimate of 25 subjects to achieve 80% power.
- In order to account for the possibility of patients dropping out prior to providing adequate pre- and post-intervention samples, we aimed to include 51 subjects in total.

- The SAS 9.4 (SAS Institute Inc.; Cary, N.C. USA) output for the sample size calculation is reported in Appendix C.

4.0 RESULTS

4.1 Patient recruitment

Patients were recruited between May 5th, 2011 and September 18th, 2013. During that time, monthly screening of the NephroCare database (a clinical database for all hemodialysis patients at The Ottawa Hospital) identified 53 patients with active prescriptions for Warfarin who met other inclusion criteria. Of those, 11 patients were subsequently excluded for the following reasons:

- Anticoagulation already managed by the thrombosis service (*n* = 4)
- Refused to meet with thrombosis service for clinical consultation to begin on the CDSS program (*n* = 1)
- Anticoagulation managed by patient's family physician (*n* = 1)
- Moved cities prior to collection of post-intervention data (*n* = 1)
- Warfarin stopped prior to post-implementation data collection due to upper gastrointestinal bleed (UGIB) with INR 4.3 (*n* = 1)
- Death due to septic and cardiogenic shock prior to post-implementation data collection (*n* = 1)
- Death presumed due to sudden cardiac death at home prior to post-implementation data collection; most recent INR had been in the therapeutic range (*n* = 1)
- Death following admission with a non-ST elevation myocardial infarction (NSTEMI) (n = *1*)

4.2 Patient characteristics

Baseline patient characteristics are detailed in Table 4. Approximately half of the 42 included patients were female. The median age (IQR) was 70 years (62 – 77). Thirty-nine patients (92.9%) were white, 1 (2.4%) was aboriginal, 1 (2.4%) was black and 1 (2.4%) was South Asian. Atrial fibrillation was the most common indication for anticoagulation (59.5%). All patients except one were being treated with heparin while on hemodialysis at the time of enrollment.

Table 4: Baseline patient characteristics

Characteristic	***n* = 42**
Female (%)	19 (45.2)
Median age in years (Interquartile range)	70 (62 – 77)
Primary indication for anticoagulation [target INR] (%)	
Atrial fibrillation [2 – 3]	25 (59.5)
Venous thromboembolism [2 – 3]	11 (26.2)
Mechanical heart valve [2.5 – 3.5]	4 (9.5)
Maintenance of dialysis catheter patency [1.5 – 2.5]	2 (4.8)
Duration of prior anticoagulation in years (%)	
< 1	21 (50)
1 - 5	17 (40.5)
> 5	4 (9.5)
Duration of prior hemodialysis in years (%)	
< 1	16 (38.1)
1 - 5	13 (30.9)
> 5	13 (30.9)
Primary cause of end-stage-renal-disease (%)	
Diabetic nephropathy	21 (50)
Ischemic nephropathy	9 (21.4)
Glomerulonephritis	6 (14.3)
Hereditary nephropathy	2 (4.8)
Obstructive uropathy	1 (2.4)
Unknown	3 (7.1)
Anti-platelet medication use (%)	
Acetylsalicylic acid (ASA)	14 (35.7)
Clopidogrel	3 (7.1)
Heparin dose on hemodialysis (%)	
≥ 1500 U/ hour	2 (4.8)
1000 U / hour	23 (54.8)
500 U / hour	16 (38.1)
None	1 (2.4)

SD, standard deviation

4.3 Patient follow-up and duration of included observation time

All patients were followed for one year after their individual enrollment date. Table 5 summarizes the duration of patient observation included for analysis due to censoring of follow-up time for the 14 days following implementation of CDSS-based management

and for procedures and hospitalizations as described in section 3.10. During the pre-intervention period, 59.5% (25/42) had all possible follow-up days included for observation (i.e. no days were censored for procedures, hospitalizations). In the post-intervention period, 35.7% (15/42) had all possible follow-up days included for observation. Overall, 16.7% (7/42) had all possible days included for observation over the one year period of study, per patient. Total included observation time was 32.8 years out of a total of 42 years of follow-up or 78.1%.

Table 5: Summary of duration of patient observation (time included for analysis)

Follow-up	**Duration**
Mean number of months included for observation over 3 month pre-intervention period (SD)	2.5 (0.84)
Mean number of post-intervention months included for observation over 9 months (SD)	6.9 (2.7)
Total pre-intervention observation in months	103.1
Total post-intervention observation in months	290.6
Total observation time in months	393.6

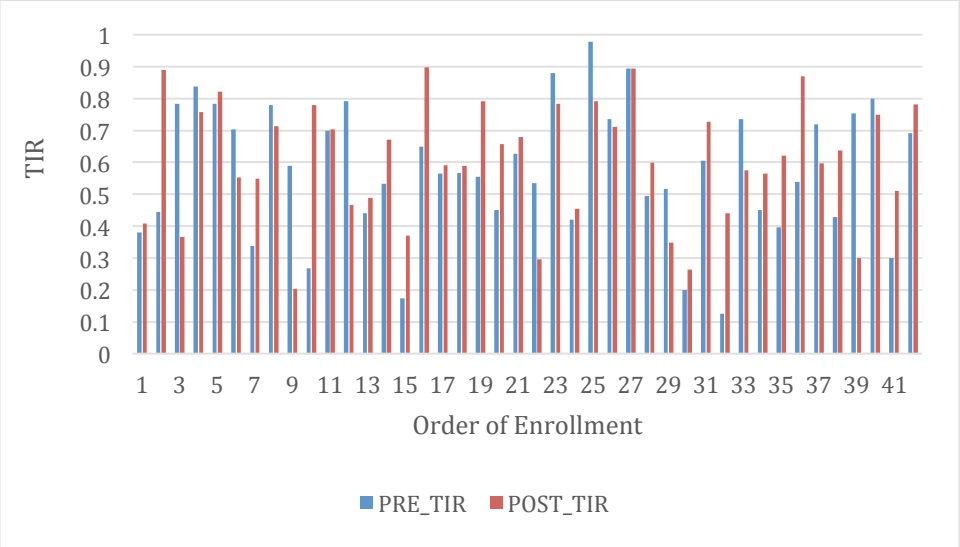
No patients were lost due to moving, transfer to peritoneal dialysis or kidney transplantation.

4.4 Evaluation of outcome measures

4.4.1 Primary outcome

The median pre-intervention TIR was 56.5% (IQR, 44.1% - 73.6%) and the median post-intervention TIR was 60.9% (IQR, 47.1% to 75.6%). The mean difference in TIR from pre- to post-intervention was 3.1%. The median difference in TIR was 3.7% (IQR, -9.5% - 20.6%; $p = 0.247$).

Figure 2: Pre- and post-intervention time-in-range according to order of enrollment.



4.4.2 Secondary outcomes

4.4.2.1 Frequency of INR testing

The pre-intervention median number of INR tests was 0.166 (IQR, 0.143 to 0.207) tests per day per patient and the post-intervention median was 0.126 (IQR, 0.091 to 0.168) tests per day per patient. The mean difference in the frequency of INR testing comparing pre- to post-intervention periods was -0.041 (SD, 0.063) tests per day per patient that is equivalent to 15 fewer tests per year per patient. The median difference between pre- and post-intervention periods was -0.040 (IQR, -0.074 to –0.0008; $P = 0.0001$) tests per day per patient.

4.4.2.2 Overall anticoagulation control

The overall (pre- and post-intervention combined) TIR was 59.1%. The overall median TIR was 59.3% (IQR, 44.9% - 75.1%). The overall mean frequency of INR testing was

0.154 tests per day. The overall median frequency of INR testing was 0.151 (IQR, 0.11 to 0.186) tests per day.

4.4.2.3 Adverse events

There were 3 deaths in the pre-intervention period (as described in Section 4.1) and 4 in the post-intervention period. No deaths were attributed to pulmonary embolism or major bleeding.

Table 6: Deaths

Study phase	**Cause of death**	***n***
Pre-intervention	Septic and cardiogenic shock	1
	Following admission with NSTEMI	1
	Presumed sudden cardiac death at home	1
Post-intervention	Sudden cardiac death	1
	Septic shock secondary to pneumonia	1
	Palliative withdrawl from dialysis treatment	2

One patient assessed for inclusion was admitted with a UGIB with INR 4.3 in the pre-intervention period (as detailed above in Section 4.1). Since the patient's warfarin was then discontinued prior to the post-intervention period, this patient was not included for analysis of primary and secondary outcomes (beyond adverse events) as this patient did not contribute post-intervention INR data.

Table 7: Major bleeding events

Pre-intervention period	**INR***
Admitted with bleeding diathesis (manifested as gingival bleeding and extensive bruising) requiring transfusion 2U PRBCs and reversal of INR. No obvious precipitant for increased INR beyond the warfarin prescription.	7.1
Post-intervention period	
Admitted with right renal hemorrhage arising from rupture of pre-existing angiomyolipoma.	2.1
Seen in ER with epistaxis; transfusion 2U PRBCs	3.5
Admitted with lower gastrointestinal bleed presumed secondary to angiodysplasia.	2.9
Seen urgently in ophthalmology clinic for decreased vision in right eye found to be secondary to intra-ocular bleeding	2.0
Admitted for epistaxis in context of thrombocytopenia due to idiopathic thrombocytopenic purpura.	1.0

*Most recent INR preceding the event

There were no confirmed VTEs in the pre- and post-intervention periods.

Two patients were evaluated for possible CVAs in the post-intervention period but neither had a confirmed CVA, TIA or RIND upon further clinical assessment including computed tomographic imaging of the head.

5.0 DISCUSSION

To our knowledge, this is the first study to evaluate the use of a pharmacist-managed, CDSS-assisted warfarin anticoagulation management strategy for hemodialysis outpatients. We found that a change from a nephrologist-led strategy to one involving the use of a CDSS resulted in a non-significant trend towards improved anticoagulation control. This study also demonstrated that the use of the CDSS-based strategy resulted in a significant reduction in the frequency of INR testing. Lastly, the risk of bleeding and thrombotic events in the pre- and post-intervention periods was similar when taking into account the longer follow-up time for the post-intervention period; however this study was not designed to perform a formal safety evaluation. Overall, the level of anticoagulation control was slightly worse amongst hemodialysis patients at The Ottawa Hospital than for what has been reported for the non-hemodialysis population on warfarin anticoagulation (as discussed below).

5.1 Comparison with previous studies

The use of CDSS-assisted maintenance warfarin dosing has been extensively evaluated for non-hemodialysis patients. Pooled analysis of 7 studies, which included 14,213 patients in total, showed a small but significant improvement in TIR with the use of a CDSS compared to not using one: mean TIR improvement was 4.5% (95%CI, 2.4% - 6.7%) (2). This accords with the difference in mean TIR of 4.1% observed for our study. Our study did show that hemodialysis patients are unlikely to benefit from CDSS-managed dosing more than unselected patients on warfarin anticoagulation given that our study had 81.5% power to detect a 10% change in TIR and did not do so. Overall, the

results are also consistent with those of much larger studies that have reported CDSS-managed maintenance warfarin dosing does not have a significant impact upon the risks of VTE, major bleeding and death for the non-HD population of patients on warfarin anticoagulation (2). Our study was not designed to, or powered to, detect a difference in clinical endpoints and given the increased risks of bleeding and thromboembolism in the HD population (as discussed in detail in section 2.1.6), it remains unclear if a lesser degree of TIR improvement might lead to a reduction in adverse events compared to what has been seen for the non-HD population. Past studies have suggested that achieving a TIR of 65% or more is associated with a reduced risk of complications (140, 178). The median TIR post-intervention of 60.9% is slightly lower than the average of 64% reported for non-HD patients managed using a nurse- or pharmacist-led anticoagulation strategy (182). There are multiple reasons why anticoagulation control may be more difficult to achieve in the HD population including frequent significant co-morbidities, nutritional deficiencies (including Vitamin K deficiency), altered pharmacokinetics due to uremia and the concurrent use of multiple medications (these issues are all discussed in detail in section 2.1.6). Nonetheless, it should be noted that due to the relatively small sample size of our study we cannot say that TIR was significantly worse than 65% for our study population given that the mean post-intervention TIR of 60.6% had a 95% CI of +/- 5.7% (not shown).

During the data-collection phase of this study, a similar study evaluating the use of an electronic nomogram for managing warfarin anticoagulation in HD-patients was reported by Thomson *et al*. (2011) (179). This before-after study compared nephrologist-led

management to management according to a nurse-led, electronic nomogram-guided strategy. The primary difference between the electronic nomogram used in their study (which is technically a form of CDSS) and the CDSS used in our study is that the CDSS we studied (DAWN AC) is able to access all past INR data and warfarin dosages for use in its algorithm as opposed to only considering recent INR results and warfarin dosages. In general, despite this minor distinction, the results of our study overall were similar to theirs. It should be noted that their study employed a different analysis strategy that utilized generalized linear mixed models (GLMMs) and included a total of 67 patients of which 40 had data available for analysis from both the pre- and post-implementation period. The use of a GLMM enabled the additional inclusion of data from patients who only had INR results recorded during either the pre- or post-implementation period. We considered a similar analysis strategy when designing the analysis for this study however the use of a GLMM relies upon several unfounded assumptions. In particular, an assumption that TIR data is normally distributed is not true. Given that TIR is a proportion, it has finite limits. The wide IQRs in our study further demonstrate that the distribution is not normal with a larger proportion of patients having excellent anticoagulation control than have equivalently terrible anticoagulation control (i.e. very high TIR *versus* very low TIRs).

Thomson *et al*. also showed that the use of the nomogram did not result in a significant change in TIR but did significantly reduce INR testing (179). They found that there were 4.7 fewer tests per patient over a five-month observation period. This reduction in INR

testing is equivalent to approximately 11 fewer tests per year per patient and is similar to our finding of approximately 15 less tests per year.

5.2 Cost implications of decreased INR testing frequency

While this study did not include an assessment of the cost-effectiveness of the intervention, there are potential cost implications to less frequent INR testing. In Ontario, the cost of a single outpatient INR test consists of a $6.20 laboratory fee plus an additional $7.76 in documentation and administration costs, for a total cost of $13.96 per test according to the Schedule of Benefits for Laboratory Services (183). As such, reducing testing in HD patients on Warfarin by 15 tests per year would result in a cost savings of $209.40 which is probably insignificant in view of the overall costs associated with HD-treatment on an annual basis. Additional cost benefits might include reduced physician and nursing time dedicated to anticoagulation management due to less frequent testing and less direct involvement with the pharmacist-led, CDSS-assisted strategy. Assuming that clinical outcomes are equivalent, as shown by our study, Thomson et al. (179) and in much larger studies in the non-HD population ((2)), potential cost benefits are balanced by the fact that the CDSS software is expensive (2): the largest cost-effectiveness study of CDSSs (which included patients managed using the DAWN AC CDSS) concluded that its use was cost-effective through the reduction of individual patient costs on a large scale (75). In the case of our study at The Ottawa Hospital where a pharmacist-led CDSS-assisted strategy was previously being employed for a larger non-HD population of patients on warfarin, the likely cost-savings justify ongoing use of this strategy for the HD-population. More generally, our findings suggest that implementation

of CDSS-assisted management of anticoagulation for HD patients can be justified if done in conjunction with a program managing the anticoagulation of a larger non-HD population rather than implementing it as a stand-alone program for a relatively small number of patients.

5.3 Study limitations

Despite slow enrollment of patients, this study achieved an adequate sample size to have detected a meaningful difference in the primary outcome had there been one. In addition, the simplicity of the design and analysis makes our findings more robust. Nonetheless, this study also has many important limitations related to its design and conduct:

5.3.1 Limitations related to before – after study design

The quasi-experimental, pre-test – post-test (before – after) study design (184, 185) is prone to threats to its internal validity but can still provide evidence that an intervention is effective, particularly when supplemented by additional data collection (186). The following sections discuss some of these threats to internal validity with respect to this study.

Regression to the mean:

Over time there is likely to be fluctuation in the mean observed TIR for HD-patients at The Ottawa Hospital relative to the the true mean. As such, if the period from which we calculated the pre-intervention TIR was a time during which the observed mean happened to be less than the true mean, odds are that subsequent evaluation of TIR (i.e. during the post-intervention period) would be increased independently of the intervention. Given that this study utilized only two assessments of TIR (before- and after-intervention), we

do not have a sense of the historical median TIR. As such, it is possible that the subsequent increase in TIR or decrease in INR test frequency that we observed results from, to some degree, regression to the mean. Notably, median TIR pre-intervention was lower than what has been reported for non-HD patients but was higher than what Thomson et al. reported for HD-units in Calgary: mean TIR for INR range 2 – 3 in their study was 51.5% (95% CI, 46.2% - 50.8%). Another factor that decreases the likelihood that regression to the mean significantly influenced our results is that pre-intervention median TIR compositely reflects 3 months of follow-up data as opposed to a single point measurement of anticoagulation control. Regression to the mean is more likely in situations in which the intervention is implemented in response to outlying data (i.e. CDSS-based management is instituted because of a drop in the TIR with nephrologist-led management in the preceding 3 months). In the case of this study, the CDSS-based intervention was not instituted in response to an identified problem with the assessed outcomes of TIR, INR testing frequency, or adverse events.

Hawthorne and placebo effects:

It is possible but unlikely that nephrologists and nurses involved in managing HD-patients' anticoagulation management altered their usual practices in such a way as to effect patients' pre-intervention TIRs. The same can be stated about the possibility of a Hawthorne effect influencing the performance of the pharmacists involved in managing anticoagulation during the post-intervention period. Given that data collection was performed using databases and this study did not have a physical presence or other reminders that it was being conducted, either in the HD-units or in the offices where the pharmacists managing the CDSS are based, any Hawthorne effect is extremely unlikely.

Similarly, it is unlikely that there was a placebo effect in which patients altered their adherence to their warfarin prescriptions after becoming aware that they were being switched to the CDSS-based strategy. Nonetheless, since all patients had a consultation with a thrombosis physician prior to being switched to the CDSS-strategy post-intervention, it is a potential confounder to our findings (e.g. the trend towards improved TIR in the post-intervention period could have resulted from thrombosis physicians emphasizing the importance of adherence to the warfarin prescription just prior to them switching to the CDSS-based dosing strategy). Any effect is likely to have been mitigated significantly by having censored the first two weeks of post-implementation data from observation and the relatively long duration of post-intervention follow-up (9 months).

Maturation threat

This threat to internal validity relates to the possibility that the outcome (e.g. improved TIR) is more attributable to changes within the group as it is observed over time (e.g. increasing age) than due to the intervention itself. The small sample size of our study does not enable meaningful statistical correction of the TIR or INR testing frequency according to age and co-morbidity (which is also likely to increase over time for HD patients). Given that the study involved only 1 year of follow-up of individual patients, maturation threat is not likely to have significantly influenced our results.

Dropout threat

Dropout threat arises when there are enough dropouts during the pre-intervention period to significantly alter the composition of those who are left for post-intervention study. If all those with very low TIRs died or had their warfarin stopped due to bleeding during the pre-intervention period, the post-TIR would be increased as a result, independently of the

intervention itself. Our method of analysis (paired assessment of the pre- and post-intervention TIR for individual patients) avoided this issue by only including patients who provided pre- and post-intervention data and by reporting all clinically significant events that occurred in the pre-intervention period for patients who were subsequently not included for TIR analysis in the post-intervention period. This would potentially have been an issue if we used GLMMs in our analysis and included data from subjects who only contributed pre-intervention TIR data.

5.3.2 Generalizability of findings

Our study population was generally similar to that of prevalent HD patients across Canada with respect to age, gender and cause of ESRD (187). Nonetheless, with respect to race/ethnic origin, minority groups were underrepresented in our study (7.1%) relative to the incident HD population in Canada from 1990 to 1998 (23%) (188), negatively affecting the generalizability of our study findings to other centres.

5.3.3 Residual confounding

Given the study design, patients acted as their own controls eliminating the need for adjustment according to baseline factors that might influence anticoagulation control. Nonetheless, as with all observational studies, this study was subject to residual confounding. Innumerable unmeasured, potentially confounding factors may have varied significantly from the pre-intervention to the post-intervention periods: e.g. medication compliance, dietary habits, and new medication use were not accounted for.

5.4 Future research

Prior to the start of this study and still continuing today, there has been controversy with respect to the use of warfarin anticoagulation for atrial fibrillation in the ESRD population. This is primarily due to conflicting results from the observational studies outlined in section 2.1.6. As a result of uncertainty regarding the safety of warfarin for ESRD patients, KDIGO 2011 guidelines were altered so as to no longer recommend warfarin anticoagulation for stroke prevention in this context (189). Similarly, the Canadian Cardiovascular Society stopped recommending warfarin for AF in dialysis patients in 2012 (190). Given current uncertainty, some experts have highlighted the need for a large-scale RCT to assess risks and benefits of warfarin anticoagulation for atrial fibrillation in patients with ESRD (191). Given high rates of incident AF in the ESRD population (115), such a study is clearly worthwhile and we echo these sentiments. Nonetheless, even if robust RCTs end up providing definitive evidence with respect to initiation of warfarin for HD patients with incident AF, many questions would remain.

One issue is that most of the HD patients on warfarin began taking it for AF prior to developing ESRD and starting on HD. This was the case for over half of the patients in our study (data not shown). Future studies to specifically characterize the risk profile for patients who have safely taken warfarin for some time prior to starting (or while being on HD) are needed to determine if a separate RCT assessing discontinuation of warfarin at the time of dialysis initiation (or afterwards) could be justified.

With respect to the use of CDSS-assisted dosing for HD patients, the optimal way to study efficacy and safety would be through a large multi-centre cluster-RCT. This is probably not realistic or necessary given that our study, Thomson et al. (2011) (179), and multiple larger studies (2) in the non-HD population have confirmed the efficacy and safety of a CDSS-based anticoagulation strategy. Broader implementation of CDSS-based anticoagulation management strategies for HD patients will depend primarily upon logistical and cost issues (as discussed above) rather then further studies assessing efficacy and safety.

CONCLUSIONS

A before – after study of anticoagulation control in HD patients on warfarin at The Ottawa Hospital demonstrated that, compared to usual anticoagulation management led by nephrologists, the implementation of a pharmacist-led, CDSS-assisted strategy was associated with a non-significant improvement anticoagulation control; however, implementation of the CDSS-assisted strategy was associated with a significant decrease in the frequency of INR testing. The use of a CDSS-assisted strategy to manage warfarin anticoagulation in HD patients at The Ottawa Hospital should be continued given the likelihood of therapeutic efficacy, equivalent safety, and the potential for cost savings. More generally, implementation of a CDSS-assisted anticoagulation strategy for HD patients should be considered at centres where a CDSS-assisted strategy already exists for managing anticoagulation in the non-HD population but may not be worthwhile as a stand-alone intervention.

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8.0 APPENDICES

8.1 APPENDIX A: Case Report Forms

The Implementation of a CDSS for Oral Anticoagulant Dosing in Hemodialysis Patients
DATA CASE REPORT FORM (complete for each patient) If data is not available then enter "000".

PART 1: DEMOGRAPHICS AND INDICATION FOR ANTICOAGULATION			
Study Participant ID#		Indication for Anticoagulation	[ ] A. fib [ ] Valve Disease [ ] Dialysis Access Line [ ] VTE [ ] Other _____
Age (years only)		First Rx for Warfarin (yyyy/mm/dd)	/ /
Sex	[ ] Male [ ] Female	Target INR	[ ] 2 to 3 [ ] Other: _____to_____
Race (as per Nephrocare)	_____	Routine Heparin Use on HD and, if Yes, Dose Used	[ ] Yes [ ] No Bolus: _____ IU Hourly: _____ IU
Site	[ ] In-Center (Riv-Gen-Civ) [ ] Satellite (OCDS-EODS-CCH-HGH-WDMH-SVH)	Cause of ESRD (as per Nephrocare)	_____
PMHx	[ ] CAD [ ] VTE [ ] GI Bleed [ ] CVA [ ] Diabetes [ ] Other bleeding _____	Date of ***first*** HD treatment (for multiple TX, first date ever) (yyyy/mm/dd)	/ /
Other Medications	[ ] ASA [ ] Dipyridamole (Aggrenox) [ ] Clopidogrel bisulfate (Plavix)		

PART 2: COMPLICATIONS OF ANTICOAGULATION AND OTHER OUTCOMES			
PRE-IMPLEMENTATION (specify and record date if yes) DATE of Pre-Review: (yyyy/mm/dd):	DATE: (yyyy/mm/dd)	**POST-IMPLEMENTATION** (specify record date if yes) DATE of Post-Review: (yyyy/mm/dd):	DATE: (yyyy/mm/dd)
Event: ☐☐☐ Adjudication Results : ☐☐		Event: ☐☐☐ Adjudication Results: ☐☐	
Event: ☐☐☐ Adjudication Results: ☐☐		Event: ☐☐☐ Adjudication Results: ☐☐	
Event: ☐☐☐ Adjudication Results: ☐☐		Event: ☐☐☐ Adjudication Results: ☐☐	
Event: ☐☐☐ Adjudication Results: ☐☐		Event: ☐☐☐ Adjudication Results: ☐☐	
Event: ☐☐☐ Adjudication Results: ☐☐		Event: ☐☐☐ Adjudication Results: ☐☐	
[ ] Death from other cause: _____		[ ] Death from other cause: _____	
[ ] Received TX [ ] Changed to PD		[ ] Received TX [ ] Changed to PD	

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CDSS STUDY – BLEEDING EVENT FORM ☐☐☐

Instructions: Complete this form for any suspected bleeding events.

1. Duration of bleeding event in days: ☐☐

2. Narrative event description: (describe all relevant info/events preceding and at the time of suspected bleeding event).
(***attach additional page if necessary***)

3. Location of suspected bleeding: Select all sites of suspected bleeding that apply

☐ Intracranial	☐ Pericardial	☐ Wound
☐ Intraspinal	☐ Intramuscular	☐ Epistaxis
☐ Intraocular	☐ Vaginal	☐ Hemoptysis
☐ Retroperitoneal	☐ Hematuria	☐ Other
☐ Intra-articilar	☐ Gastrointestinal	Specifiy:_____

5. Admitted to hospital? ☐ Yes ☐ No

If yes, duration of admission: ☐☐☐ days

6. Was an intervention performed? (check all that apply)

☐ surgical ☐ endoscopic ☐ pharmacological ☐ nil

7. Most recent pre-bleed hemoglobin ☐☐☐ g/dL

8. Lowest post-bleed hemoglobin ☐☐☐ g/dL
☐ Not done

CDSS STUDY – BLEEDING EVENT FORM ☐☐☐

9. Transfusion ☐ None **OR** Indicate **all** blood products transfused and the **total** number of units

☐ Whole blood: __ units	☐ Fresh frozen plasma (FFP): ____units
☐ Prothrombin complex: ____ units	☐ Platelets: ____ units
☐ Red cells: _____ units	☐ VIIa: _____ units
	☐ Other: *type and amount* _____

10. Diagnostic tests that may have revealed or confirmed the bleeding site or cause:

☐ None **OR**

Indicate **all** objective testing performed (attach copies of all reports with names and dates removed)

☐ CT scan
☐ Ultrasound
☐ MRI
☐ Endoscopy

11. Did the bleeding cause discomfort (e.g. pain)?

☐ YES ☐ NO ☐ Unknown

If *yes*, provide details: _____

12. Did the bleeding cause impairment of activities of daily living?

☐ YES ☐ NO ☐ Unknown

If *yes*, provide details: _____

13. Investigator's judgement of bleed severity?

☐ Major Bleeding ☐ Clinically relevent Non-Major Bleeding ☐ Minor Bleeding

Investigator Name: _____

Investigator's Signature: _____

CDSS STUDY – BLEEDING EVENT FORM ☐☐☐

Bleeding Definitions

Major Bleeding

A bleed will be categorized as being major if it fulfils at least one of the following criteria:

1. Fatal bleeding

OR

2. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome

AND/OR

3. Bleeding causing a fall in hemoglobin level of 20 g L^{-1} (1.24 mmol L^{-1}) or more, or leading to transfusion of two or more units of whole blood or red cells.

Clinically Relevant Non-major Bleeding:
These are defined as overt bleeding episodes not meeting the inclusion for major bleeding but associated with at least **one** of the following:

- Hospitalization;
- Medical intervention;
- Unscheduled contact with a physician;
- Associated with discomfort for the patient such as pain, or impairment of activities of daily life.

Minor Bleeding
Minor bleeding will be defined as a clinically overt bleeding event that does not meet the criteria for either a major bleeding event or a clinically relevant non-major bleeding event.

Adjudication Results:

☐ Major bleeding

☐ Clinically relevant, non-major bleeding

☐ Minor bleeding

Adjudicator 1: _____ | _____ | _____
Print Name | Signature | Date (dd/mmm/yyyy)

Adjudicator 2: _____ | _____ | _____
Print Name | Signature | Date (dd/mmm/yyyy)

CDSS STUDY – SUSPECTED CVA / ARTERIAL THROMBOSIS FORM ☐☐☐

Type of event

Possible Stroke ☐ YES ☐ NO ☐ UNKNOWN

Defined as a sudden onset of neurological deficit that persists for more than 24 hours and involves one or more of the following:

i. Hemiparesis; involving face, arm and/or leg unilaterally ☐ YES ☐ NO ☐ UK
ii. Hemisensory loss; involving face, arm and/or leg unilaterally ☐ YES ☐ NO ☐ UK
iii. Speech impairment; (ie. aphasia) ☐ YES ☐ NO ☐ UK
iv. Visuo–spatial impairment ☐ YES ☐ NO ☐ UK
v. Visual Loss (monocular or binocular) ☐ YES ☐ NO ☐ UK
vi. Two or more of the following symptoms which suggest vertebrobasilar involvement:
   a. Incoordination/ataxia ☐ YES ☐ NO ☐ UK
   b. Cranial nerve abnormality; ☐ YES ☐ NO ☐ UK
   c. Dysarthria; ☐ YES ☐ NO ☐ UK
   d. Dysphagia ☐ YES ☐ NO ☐ UK
   e. Vertigo ☐ YES ☐ NO ☐ UK
   f. Reduction/loss of consciousness ☐ YES ☐ NO ☐ UK
   g. Diplopia ☐ YES ☐ NO ☐ UK
vii. Objective and persistent (> 1 week) worsening of a previous deficit or worsening associate with an appropriate new finding on CT scan or MRI ☐ YES ☐ NO ☐ UK

3.1 Investigations for suspected Stroke

	TEST	DONE	DATE (DD-MM-YYYY)	RESULT	SPECIFICATION
3.1.1	CT Scan (HEAD) (**Initial scan**)	☐ Not Done ☐ Done	|__|__||__|__||__|__|__|__|	☐ Normal ☐ Abnormal	☐ Same as previous scan ☐ Worsening of previous defect ☐ New defect ☐ No previous scan to compare to
3.1.2	Repeat CT (HEAD) (**if more than 1 repeat scan provide results for most diagnostic scan)**	☐ Not Done ☐ Done	|__|__||__|__||__|__|__|__|	☐ Normal ☐ Abnormal	☐ Same as previous scan ☐ Worsening of previous defect ☐ New defect ☐ No previous scan to compare to

CDSS STUDY – SUSPECTED CVA / ARTERIAL THROMBOSIS FORM ☐☐☐

3.1.3	MRI (BRAIN)	☐ Not Done ☐ Done	|__|__||__|__||__|__|__|__|__|	☐ Normal ☐ Abnormal	☐ Same as previous scan ☐ Worsening of previous defect ☐ New defect ☐ No previous scan to compare to

3.2 Final Assessment (to be completed by adjudicators):

Acute Stroke? ☐ YES ☐ NO

4. Stroke treatment

Was subject treated for acute stroke? ☐ YES ☐ NO ☐ UK

If yes, specify:

thrombolytic therapy - tPA ☐ YES ☐ NO ☐ UK

heparin therapy ☐ YES ☐ NO ☐ UK

carotid endarterectomy ☐ YES ☐ NO ☐ UK

antiplatelet therapy – ASA ☐ YES ☐ NO ☐ UK

Plavix ☐ YES ☐ NO ☐ UK

Other, specify: _____

Other treatment: _____

CDSS STUDY – SUSPECTED CVA / ARTERIAL THROMBOSIS FORM ☐☐☐

Suspected Transient Ischemic Attack ☐ YES ☐ NO ☐ UK

Defined as a sudden onset of a neurologic deficit lasting at least 1 minute but lasting < 24 hours. (Isolated syncope will not be considered a TIA unless this occurs with other neurological symptoms suggesting vertebrobasilar involvement.)

Hemiparesis; involving face, arm and/or leg unilaterally ☐ YES ☐ NO ☐ UK

i. Hemisensory loss; involving face, arm and/or leg unilaterally ☐ YES ☐ NO ☐ UK
ii. Speech impairment; (ie. aphasia) ☐ YES ☐ NO ☐ UK
iii. Visuo–spatial impairment ☐ YES ☐ NO ☐ UK
iv. Visual Loss (monocular or binocular) ☐ YES ☐ NO ☐ UK
v. Two or more of the following symptoms which suggest vertebrobasilar involvement:
   a. Incoordination/ataxia ☐ YES ☐ NO ☐ UK
   b. Cranial nerve abnormality; ☐ YES ☐ NO ☐ UK
   c. Dysarthria; ☐ YES ☐ NO ☐ UK
   d. Dysphasia ☐ YES ☐ NO ☐ UK
   e. Vertigo ☐ YES ☐ NO ☐ UK
   f. Reduction/loss of consciousness ☐ YES ☐ NO ☐ UK
   g. Diplopia; ☐ YES ☐ NO ☐ UK
   viii. Other (please describe): _____

_____

5.1 **If recorded, indicate the length of time the symptom lasted:**

Specify symptom: _____: ___ ___ minutes or ___ ___ hours
Specify symptom: _____: ___ ___ minutes or ___ ___ hours
Specify symptom: _____: ___ ___ minutes or ___ ___ hours
Specify symptom: _____: ___ ___ minutes or ___ ___ hours

5.2 **Investigations for suspected TIA**

	TEST	DONE	RESULT	SPECIFICATION
5.2.1	CT Scan **(Initial scan)**	☐ Not Done ☐ Done	☐ Normal ☐ Abnormal	☐ Same as previous scan ☐ Worsening of previous defect ☐ New defect ☐ No previous scan to compare to
5.2.2	CT Scan **(if more than 1 repeat scan provide**	☐ Not Done ☐ Done	☐ Normal ☐ Abnormal	☐ Same as previous scan ☐ Worsening of

CDSS STUDY – SUSPECTED CVA / ARTERIAL THROMBOSIS FORM ☐☐☐

	results for most diagnostic scan)			☐ New defect ☐ No previous scan to compare to
5.2.3	MRI	☐ Not Done ☐ Done	☐ Normal ☐ Abnormal	☐ Same as previous scan ☐ Worsening of previous defect ☐ New defect ☐ No previous scan to compare to

5.3 Final assessment (to be completed by adjdicators): Acute TIA? ☐ YES ☐NO

6. TIA treatment

Was subject treated for acuteTIA? ☐ YES ☐ NO ☐ UK

If yes, specify:

heparin therapy ☐ YES ☐ NO ☐ UK

antiplatelet therapy: ASA ☐ YES ☐ NO ☐ UK

Plavix ☐ YES ☐ NO ☐ UK

Other, specify _____

carotid endarterectomy ☐ YES ☐ NO ☐ UK

Other treatment ☐ YES ☐ NO ☐ UK

Specify: _____

CDSS STUDY – SUSPECTED CVA / ARTERIAL THROMBOSIS FORM ☐☐☐

Suspected Peripheral Embolism – occurrence of acute ischemia documented by angiography or at surgical removal. ☐ **YES** ☐ **NO** ☐ **UK**

9.1 Investigations for suspected Peripheral Embolism

	TEST	DONE	RESULT	SPECIFICATION
9.1.1	Angiography	☐ Not Done ☐ Done	☐ Normal ☐ Abnormal	☐ Same as previous ☐ Worsening of previous ☐ New defect ☐ No previous to compare to

9.2 Final assessment (adjudicators): Acute Peripheral Embolism diagnosed?
☐ **YES** ☐ **NO**

Peripheral Embolism Treatment

Was subject treated for acute peripheral embolism? ☐ **YES** ☐ **NO** ☐ **UK**

If yes, specify:

Thrombolytic therapy ☐ **YES** ☐ **NO** ☐ **UK**
Surgical removal ☐ **YES** ☐ **NO** ☐ **UK**
Other treatment ☐ **YES** ☐ **NO** ☐ **UK**

Specify: _____

CDSS STUDY – SUSPECTED CVA / ARTERIAL THROMBOSIS FORM ☐☐☐

Suspected Valve Thrombosis

☐ YES ☐ NO ☐ UK

Defined as thrombosis deposition on the valve resulting in valve dysfunction requiring re-operation or thrombolytic therapy.

11.1 Investigations for suspected Valve Thrombosis

	TEST	DONE	RESULT	SPECIFICATION
11.1.1	Angiography	☐ Not Done ☐ Done	☐ Normal ☐ Abnormal	☐ Same as previous ☐ Worsening of previous ☐ New defect ☐ No previous to compare to
11.1.2	Echo-cardiogram	☐ Not Done ☐ Done	☐ Normal ☐ Abnormal	☐ Same as previous ☐ Worsening of previous ☐ New defect ☐ No previous to compare to

Final assessment (adjudicators): Acute Valve Thrombosis diagnosed? ☐ YES ☐ NO

Valve Thrombosis Treatment

Was subject treated for acute valve thrombosis: ☐ YES ☐ NO ☐ UK

If yes, specify:

Thrombolytic therapy ☐ YES ☐ NO ☐ UK
Surgical removal ☐ YES ☐ NO ☐ UK
Other treatment ☐ YES ☐ NO ☐ UK

Specify: _____

CDSS STUDY – SUSPECTED CVA / ARTERIAL THROMBOSIS FORM ☐☐☐

Adjudication Results:

Thrombotic Event:

- ☐ CVA
- ☐ TIA
- ☐ Peripheral arterial thrombosis
- ☐ Valvular thrombosis
- ☐ NONE

Adjudicator 1: _____ | _____ | _____
Print Name | Signature | Date (dd/mmm/yyyy)

Adjudicator 2: _____ | _____ | _____
Print Name | Signature | Date (dd/mmm/yyyy)

CDSS STUDY – SUSPECTED VTE FORM ☐☐☐

DVT Signs & Symptoms:					
Edema	☐ Rt. Leg	☐ Lt. Leg	☐ Both Legs	☐ None	☐ Unknown
Swelling	☐ R. Leg	☐ Lt. Leg	☐ Both Legs	☐ None	☐ Unknown
Tenderness	☐ Rt. Leg	☐ Lt. Leg	☐ Both Legs	☐ None	☐ Unknown
Redness	☐ Rt. Leg	☐ Lt. Leg	☐ Both Legs	☐ None	☐ Unknown
Discomfort	☐ Rt. Leg	☐ Lt. Leg	☐ Both Legs	☐ None	☐ Unknown

Did any of the DVT signs/symptoms last longer than one month? ☐ Yes* ☐ No ☐ Unknown
* If "Yes", please check all that apply: ☐ Edema ☐ Swelling ☐ Tenderness ☐ Redness ☐ Discomfort

PE Signs/Symptoms:			
Tachypnea	☐ Yes	☐ No	☐ Unknown
Tachycardia	☐ Yes	☐ No	☐ Unknown
Hemoptysis	☐ Yes	☐ No	☐ Unknown
Chest Pain	☐ Yes	☐ No	☐ Unknown
Shortness of Breath	☐ Yes	☐ No	☐ Unknown
Presyncope/Syncope	☐ Yes	☐ No	☐ Unknown

Did any of the PE signs/symptoms last longer than one month? ☐ Yes* ☐ No ☐ Unknown
* If "Yes", please check all that apply:
☐ Tachypnea ☐ Tachycardia ☐ Hemoptysis ☐ Chest Pain ☐ Shortness of Breath ☐ Presyncope/Syncope

Risk factors for VTE within the month prior to event:

☐ Hospitalization ☐ Lower Limb Cast ☐ Newly diagnosed cancer ☐ Surgery

Imaging for DVT:

Compression Ultrasound: (Duplicate form for serial imaging)	
☐ Done ☐ Not Done	Ultrasound Result: ☐ Non-compressible segment – same as prior imaging ☐ Non-compressible segment – new or no prior imaging ☐ Normal ☐ Inconclusive
Venogram or MRV:	
☐ Done ☐ Not Done	Venogram or MRV Result: ☐ Normal ☐ Intraluminal filling defect – same as prior imaging ☐ Intraluminal filling defect – new or no prior imaging ☐ Inconclusive

If DVT confirmed by imaging, specify location of all thrombosed veins:

☐ Trifurcation of popliteal vein	☐ Iliac vein	☐ Cerebral vein
☐ Popliteal vein	☐ Inferior Vena Cava	☐ Arm vein
☐ Femoral vein	☐ Portal vein	☐ Other:_____

Please check one of the boxes below for patients who DID NOT have a proximal DVT:

☐ Distal DVT (below trifurcation of popliteal vein)	☐ Superficial Phlebitis	☐ None

CDSS STUDY – SUSPECTED VTE FORM ☐☐☐

Imaging for PE:

VQ Scan:	
☐ Done ☐ Not Done	VQ Scan Result: ☐ Perfusion Defect – same as prior imaging ☐ Perfusion Defect – new or no prior imaging ☐ *low probability* ☐ *intermediate probability* ☐ *high probability* ☐ Normal/near normal ☐ Inconclusive
CT Scan:	
☐ Done ☐ Not Done	CT Scan Result: ☐ Intraluminal Filling Defect – same as prior imaging ☐ Intraluminal Filling Defect – new or no prior imaging *(specify location of most proximal artery)* ☐ *main pulmonary artery* ☐ *lobar pulmonary artery* ☐ *segmental pulmonary artery* ☐ *sub-segmental pulmonary artery* ☐ Normal ☐ Inconclusive

D-dimer: ☐ Done ☐ Not Done

Result: ☐ Positive ☐ Negative or record actual value : _____

Local Investigator's judgement of VTE

☐ No symptomatic VTE
☐ Symptomatic distal DVT only (below trifurcation)
☐ Symptomatic proximal DVT (trifurcation or above)
☐ Symptomatic sub-segmental PE
☐ Symptomatic PE (segmental or greater)
☐ DVT
☐ Superficial Phlebitis
☐ Unusual Site VTE
☐ Asymptomatic distal DVT on Day 21 study u/s
☐ Asymptomatic proximal DVT on Day 21 study u/s

VTE Cause(defined on following page)**:** ☐ Provoked ☐ Unprovoked

Please note: imaging results and blood test results must be de-identified and attached for adjudication committee.

Investigator Name: _____

Investigator's Signature: _____

CDSS STUDY – SUSPECTED VTE FORM ☐☐☐

Diagnostic Criteria for DVT and PE	
The objective criteria considered diagnostic for a DVT: ▪ Venography demonstrating a constant intraluminal filling defect in the deep veins above the trifurcation of the popiteal vein. Venograms will be considered adequate for diagnosis of a DVT if the entire deep venous system can be seen to the level of the common femoral vein. ▪ Compression ultrasound revealing a non-compressibility of a venous segment above the trifurcation of the popliteal vein. ▪ Below the knee DVT, diagnosed by either venography or compression ultrasound	The objective criteria considered diagnostic for PE: ▪ Pulmonary angiography demonstrating a constant intraluminal filling defect or a cut-off of a vessel > 2.5 mm in diameter ▪ V/Q scan indicating high-probability ▪ PE found at autopsy

Adjudication Results:	
Suspected VTE (DVT or PE)	**VTE Type (Check all that apply):** ☐ No symptomatic VTE ☐ Symptomatic distal DVT only (below trifurcation) ☐ Symptomatic proximal DVT (trifurcation or above) ☐ Symptomatic sub-segmental PE ☐ Symptomatic PE (segmental or greater) ☐ DVT ☐ Superficial Phlebitis ☐ Unusual Site VTE ☐ Asymptomatic distal DVT on Day 21 Study ultrasound ☐ Asymptomatic proximal DVT on Day 21 Study Ultrasound
	VTE Cause: ☐ Provoked (*leg fracture or lower extremity plaster cast; immobilization for > 3 days; surgery with general anesthetic < 3 months prior to index VTE event; diagnosis of malignancy in <5 years.)* ☐ Unprovoked (a*ny VTE that occurs outside of the periods listed above)*

Adjudicator 1: _____ | _____ | _____
Print Name | Signature | Date (dd/mmm/yyyy)

Adjudicator 2: _____ | _____ | _____
Print Name | Signature | Date (dd/mmm/yyyy)

CDSS STUDY – DEATH EVENT FORM ☐☐☐

Narrative event description: (describe all relevant info/events preceding and at the time of death)

(Attach additional page if necessary)

Primary Cause of Death	
☐ Pulmonary Embolism	☐ Respiratory Disease
☐ Myocardial Infarction	☐ Major Bleeding
☐ Stroke	☐ Trauma
☐ Congestive Heart Failure	☐ Unknown
☐ Cancer	☐ Other:_____
Secondary Cause of Death	
☐ Pulmonary Embolism	☐ Cancer
☐ Myocardial Infarction	☐ Trauma
☐ Stroke	☐ Congestive Heart Failure
☐ Respiratory Disease	☐ Unknown of Not Applicable
☐ Major Bleeding	☐ Other:_____

Source documentation available (*indicate all available documents related to the death and attach if applicable, with names and dates removed):*

☐ Hospital Discharge Summary
☐ Hospital Chart Notes
☐ Death Certificate
☐ Other, specify: _____

Was a autopsy performed?
☐ Yes (attache copy of report with name and dates removed)
☐ No

Investigator Name: _____

Investigator's Signature: _____

CDSS STUDY – DEATH EVENT FORM ☐☐☐

Adjudication Results:

Primary cause of death:

- ☐ Pulmonary embolism
- ☐ Major bleeding
- ☐ Other

Indicate certainty that Pulmonary Embolism was the primary cause of death:

- ☐ Certain: Hypotension, hypoxia, cardiac arrest with no other expanation other than PE and autopsy or radiographic confirmation
- ☐ Highly Probable: criteria for certain but another disease could have caused the death
- ☐ Probable: other cause suspected based on clinical evidence but 100% certainty not available
- ☐ Unlikely: all other cases

Adjudicator 1: _____ | _____ | _____
Print Name | Signature | Date (dd/mmm/yyyy)

Adjudicator 2: _____ | _____ | _____
Print Name | Signature | Date (dd/mmm/yyyy)

8.2 APPENDIX B: Ottawa Hospital Research Ethics Board Documentation

Ottawa Hospital Research Ethics Boards / Conseils d'éthique en recherches
725 Parkdale Avenue, Box 411, Ottawa, Ontario K1Y 4E9 613-798-5555 ext. 14902 Fax: 613-761-4311
http://www.ohri.ca/ohreb

January 7, 2011

Dr. Edward Clark

[redacted]

Dear Dr. Clark:

Re: Protocol # 2010680-01H **The Implementation of a Computerized Decision Support System for Oral Anticoagulant Dosing in Hemodialysis Patients: An Observational Study of Effectiveness and Safety in a High-Risk Population**

Protocol approval valid until - January 6, 2012

Thank you for your letter of December 16, 2010. I am pleased to inform you that this protocol underwent expedited review by the Ottawa Hospital Research Ethics Board (OHREB) and is approved. No changes, amendments or addenda may be made to the protocol without the OHREB's review and approval.

Approval is for the following:
- Data Case Report Form, received November 08, 2010

If the study is to continue beyond the expiry date noted above, a Renewal Form should be submitted to the OHREB approximately six weeks prior to the current expiry date. If the study has been completed by this date, a Termination Report should be submitted.

TCPS 2 has immediately replaced the 1st edition of the Policy as the official human research ethics policy of the Agencies. The REB approvals will not be withheld from now until the on-line tutorial for Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS) 2nd Edition becomes available. The TCPS 2 on-line tutorial should be available in February 2011. We will communicate an education session in January for TCPS 2 and announce the date for activation of the Council's on-line tutorial in February as soon as we are made aware

If you or other members of your research team are currently involved in a research study, you should read the full TCPS 2 and document your self-training on your training record and in your CV. If you have already completed the on-line tutorial for TCPS 1, please refer to the email of December 13, 2010, and document your self-training after reviewing the summary of changes between the TCPS 1 and TCPS 2. The key point to consider is whether you and/or your team members have the appropriate training (documented) for the work assigned before starting the research study.

The Ottawa Hospital Research Ethics Board is constituted in accordance with, and operates in compliance with the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans; Health Canada Good Clinical Practice: Consolidated Guideline; Part C Division 5 of the Food and Drug Regulations of Health Canada; and the provisions of the Ontario Health Information Protection Act 2004 and its applicable Regulations.

Raphael Saginur, M.D.
Chairman
Ottawa Hospital Research Ethics Board

RS/hm

Ottawa Hospital Research Ethics Boards / Conseils d'éthique en recherches

725 Parkdale Avenue, Box 411, Ottawa, Ontario K1Y 4E9 613-798-5555 ext. 14902 Fax: 613-761-4311
http://www.ohri.ca/ohreb

January 5, 2012

Dr. Edward Clark
[redacted]

Dear Dr. Clark:

RE: Protocol# - 2010680-01H **The Implementation of a Computerized Decision Support System for Oral Anticoagulant Dosing in Hemodialysis Patients: An Observational Study of Effectiveness and Safety in a High-Risk Population**

Renewal Expiry Date - January 6, 2013

I am pleased to inform you that your Annual Renewal Request (listed above) was reviewed by the Ottawa Hospital Research Ethics Board (OHREB) and is approved. No changes, amendments or addenda may be made in the protocol without the OHREB's review and approval.

Renewal is valid for a period of one year. Approximately one month prior to that time, a single renewal form should be sent to the OHREB office.

The Tri-Council Policy Statement requires a greater involvement of the OHREB in studies over the course of their execution. As well, you must inform the Board of adverse events encountered during the study, here or elsewhere, or of significant new information which becomes available after the Board review, either of which may impinge on the ethics of continuing the study. The OHREB will review the new information to determine if the protocol should be modified, discontinued, or should continue as originally approved.

Yours sincerely,

[redacted]

Raphael Saginur, M.D.
Chairman
Ottawa Hospital Research Ethics Board

/kd

Ottawa Hospital Research Ethics Boards / Conseils d'éthique en recherches
725 Parkdale Avenue, Box 411, Ottawa, Ontario K1Y 4E9 613-798-5555 ext 14002 Fax: 613 761-4311
http://www.ohri.ca/ohreb

Dr. Edward Clark
[redacted]

Dear Dr. Clark:

RE: Protocol# - 2010680-01H **The Implementation of a Computerized Decision Support System for Oral Anticoagulant Dosing in Hemodialysis Patients: An Observational Study of Effectiveness and Safety in a High-Risk Population**

Renewal Expiry Date - January 06, 2014

I am pleased to inform you that your Annual Renewal Request (listed above) was reviewed by the Ottawa Hospital Research Ethics Board (OHREB) and is approved. No changes, amendments or addenda may be made in the protocol without the OHREB's review and approval.

Renewal is valid for a period of one year. Approximately one month prior to that time, a single renewal form should be sent to the OHREB office.

The Tri-Council Policy Statement requires a greater involvement of the OHREB in studies over the course of their execution. As well, you must inform the Board of adverse events encountered during the study, here or elsewhere, or of significant new information which becomes available after the Board review, either of which may impinge on the ethics of continuing the study. The OHREB will review the new information to determine if the protocol should be modified, discontinued, or should continue as originally approved.

Yours sincerely,

[redacted]

Raphael Saginur, M.D.
Chairman
Ottawa Hospital Research Ethics Board

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8.3 APPENDIX C: SAS Power Calculation Output

The SAS System

The POWER Procedure
Paired t Test for Mean Difference

Fixed Scenario Elements

Distribution	Normal
Method	Exact
Mean Difference	0.1
Standard Deviation	0.17
Correlation	0.15
Number of Sides	2
Null Difference	0
Alpha	0.05

Computed N Pairs

Index	Nominal Power	Actual Power	N Pairs
1	0.6	0.617	27
2	0.7	0.710	33
3	0.8	0.805	41
4	0.9	0.902	54

9.0 ACKNOWLEDGEMENTS

I thank Dr. Greg Knoll and Dr. Marc Rodger for their expert guidance and supervision throughout this project.

I thank Dr. Tim Ramsay for advice and expertise that shaped the design of this project.

I thank Jessica Wagner, Judy Cheeseman, Scott Mullen, Edita Delic and Hannah Trottier for dedicated assistance with data collection for this project.

I thank the Department of Medicine at The Ottawa Hospital for providing funding for this project.

Most of all, I thank Alex for her patience and support during the (prolonged) completion of this project.