Risk and Benefit of Warfarin for Primary Prevention in Atrial Fibrillation Patients on Hemodialysis:
A Retrospective Pilot Study

Alexandra Andrei, PharmD [1] Abdulkadir A. Hussein, PhD [2] Joseph Zagar, PharmD [1] Derrick Soong, PharmD [1]

1. Windsor Regional Hospital on Ouellette, 1030 Ouellette Avenue, Windsor, Ontario, Canada
2. University of Windsor, Faculty of Mathematics, 401 Sunset Avenue, Windsor, Ontario, Canada

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[1]Windsor Regional Hospital, Windsor, ON, [2]University of Windsor, ON

Rationale: Although warfarin is an established anticoagulation therapy for prevention of ischemic strokes in patients with atrial fibrillation, studies reporting INR values with correlation to warfarin efficacy and safety outcomes in patients on hemodialysis with atrial fibrillation are scarce. The purpose of this study was provide additional information to aid in optimizing future clinical anticoagulation decisions for patients with atrial fibrillation on hemodialysis.

Methods: A retrospective cohort study was conducted from April 2011 to January 2019 at a regional kidney dialysis centre in southwestern Ontario, Canada. The primary objective of this study was to correlate achieved INR measurements with the efficacy and safety of warfarin anticoagulation.

Results: A total of 286 patients were reviewed and 25 patients were included. No ischemic strokes were reported and six bleeding episodes occurred. The mean INR of the 25 patients was 2.4 (SD±0.47) with an average follow up of 336 days. Using a Cox Proportional Hazards Model, univariate correlations between risk of bleeding and baseline characteristics were examined and no statistically significant correlations were found.

Conclusion: Patients on hemodialysis with atrial fibrillation may have a higher bleeding rate while on warfarin despite having therapeutic INRs. This may be attributed to the small sample size, duration of observation and factors such as intra-dialysis heparin use and uremic platelet dysfunction. Therefore, initiating warfarin for primary prevention in this patient population requires a careful assessment of bleeding risk factors. Further studies are warranted.

INTRODUCTION

In patients with end stage chronic kidney disease (defined as an eGFR <15 mL/min/1.73 m^2) requiring hemodialysis with the additional diagnosis of atrial fibrillation, the risk-to-benefit of using warfarin for primary prevention of adverse events due to atrial fibrillation is unclear. Patients on hemodialysis with atrial fibrillation pose a paradox to clinicians because concurrently they are at a high risk of a thrombotic event as well as a bleeding event.[1] Despite the higher risk for cardioembolic strokes due to atrial fibrillation, chronic kidney disease is associated with a prothrombotic state due to abnormalities in clotting factors and an underlying inflammatory state placing patients at up to ten times higher risk of adverse clotting events. Furthermore, patients with end stage renal disease are at a higher risk of bleeding events due to

impairment in renal clearance of uric acid which leads to platelet dysfunction.[1,2,3]

CHADS$_2$ and CHA$_2$DS$_2$-VASc risk assessment scores are used to stratify the risk for stroke in patients with atrial fibrillation.[2] However, patients with chronic kidney disease were underrepresented in studies that validated the CHADS$_2$ and CHA$_2$DS$_2$-VASc risk tools and as such are not currently included in the risk scores` criteria. This makes assessment of stroke risk difficult in patients with atrial fibrillation and hemodialysis.[1] Bleeding rates in this patient group are difficult to ascertain from current literature as studies may use various definitions for bleeding events. At present, the study reported rate of bleeding events for patients on hemodialysis with fibrillation varies from 2.5-54% per year.[1,3]

The current Canadian and American clinical practice guidelines provide different recommendations with respect to this specific patient population. The 2012 Canadian Cardiovascular Society Atrial Fibrillation Guidelines do not routinely recommend anticoagulation with warfarin in patients with atrial fibrillation and hemodialysis due to a lack of evidence. In contrast, the 2014 *American Heart Association*/American College of Cardiology Guidelines for Atrial Fibrillation recommend warfarin anticoagulation for patients with a CHA$_2$DS$_2$-VASc score of 2 or greater and who have end-stage chronic kidney disease or are on hemodialysis. However, the data for this recommendation has been derived from a single study.[2,4]

Evidence evaluating the safety and efficacy of warfarin in this specific patient population shows conflicting results. Of greater importance, International Normalized Ratio (INR) data which is used to assess warfarin degree of anticoagulation has not been provided or accurately monitored in studies published to date. Current studies have not correlated outcomes with INR targets and CHADS2 scores.[5] Further, information from the International Dialysis Outcomes and Practice Patterns Study (DOPPS) cohort study showed oral anticoagulation in patients with hemodialysis increased major bleeding events, all cause and cardiovascular mortality. However, DOPPS highlighted as a significant limitation the lack of INR measurements, as well as a lack of assessing warfarin adherence since patient information was collected on an outpatient basis.[6]

At present time there is a conflicting body of evidence regarding warfarin therapy for primary prevention in patients with atrial fibrillation on hemodialysis. The degree of risk and/or benefit of warfarin in this patient population cannot be accurately determined without assessing how efficacy and safety clinical outcomes relate to reaching INR targets. This study will be a pilot study to collect INR data and identify the correlation between the achieved INR targets and risk and benefit associated with warfarin use in this patient population. The ultimate goal of this study is to provide additional information to aid in optimizing future clinical anticoagulation decisions for patients with atrial fibrillation on hemodialysis.

METHODS

Design

Upon Research Ethics Board clearance, a retrospective chart review was conducted at a regional kidney dialysis centre in southwestern Ontario, Canada between April 1, 2011 and January 31, 2019. This specific time frame was selected to incorporate all available warfarin dosing records for patients that met the inclusion criteria. Patients were included in the study if they met all of the following: (1) patient at least 18 years old, (2) patient on hemodialysis, (3) patient with a diagnosis of atrial fibrillation, (4) received warfarin for primary prevention of ischemic stroke. Patients were excluded if they: (1) were pregnant, (2) under the age of 18 years old, (3) had concurrent venous thromboembolism, (4) received concurrent chemotherapy, (5) had a history of transient ischemic attack and/or cerebrovascular accident, (6) had valvular atrial fibrillation with an INR target of 2.5 to 3.5, (7) received chronic NSAIDs and/or corticosteroids and/or antiplatelet agents defined as use of one of the above agents for more than 30 days, (8) received warfarin for less than seven days, (9) had other concurrent indications for warfarin use, (10) were on peritoneal dialysis.

Definitions

The patient data was collected from individual electronic records and maintained in a computerized spreadsheet. Pharmacists monitored INR values minimum weekly and more frequently if required then adjusted warfarin dose requirements accordingly. Information collected by the pharmacists adjusting the warfarin dosage included INR values, hemoglobin, platelets, serum creatinine, pertaining drug interactions, changes in diet and other relevant information such as upcoming procedures.

The following outcomes were tracked for each patient from the initiation of warfarin to either discontinuation of warfarin, death or end of study period ie. January 31, 2019: major bleeding events, minor bleeding events and ischemic strokes. Bleeding events were defined in accordance to the International Society on Thrombosis and Haemostasis.[7,8]

Major bleeding was defined as: (1) fatal bleeding; and/or (2) symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome; and/or (3) bleeding causing a fall in hemoglobin level of 20 g/L or more or leading to transfusion of two or more units of whole blood or red cells.[7] Minor bleeding was defined as: any sign or symptom of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that would not fit the criteria for the definition of major bleeding but does meet at least one of the following criteria: (1) requiring medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, (3) prompting a face to face evaluation.[8] Ischemic strokes were diagnosed based on documentation on CT scan.

The primary endpoint focused on investigating the correlation between achieved INR measurements at this institution with the efficacy and safety of warfarin anticoagulation to prevent thromboembolism due to atrial fibrillation in a local hemodialysis population.

Data Analysis

Data were analyzed using a repeated measures ANOVA statistical method. Basic descriptive statistics were performed to describe the sample characteristics. A Cox Proportional Hazards Model was performed to examine the univariate correlations between the risk of bleeding and the patients' baseline characteristics.

RESULTS

Sample Characteristics

A total of 286 charts were reviewed and 25 patients met the inclusion criteria. Table 1 displays the patients' baseline characteristics. The results indicate the average age in the sample was 77.4 years old with a SD±7 years. Females comprised 48% (n=12) of the sample. The following CHADS$_2$ risk factors were identified for all included patients: congestive heart failure, hypertension, and diabetes. In addition, the use of ACEi, ARB and β-Blocker medications were identified for each patient because these agents can impact long term mortality and blood pressure control.

INR Values and Outcome Analysis

The mean follow up time from warfarin initiation was 336 (SD±401) days with a minimum of 19 days and a maximum of 1688 days. Figure 1 illustrates the distribution of the mean INR measurements for the 25 patients. Over the follow up period from warfarin initiation to the last documented INR found in the patient's chart, the average INR for the 25 patients was 2.4 (SD±0.47) with a minimum value of 1.7 and a maximum value of 4.1. The Kaplan Mayer Survival Curve in Figure 2 illustrates the median time to bleeding was estimated to be 1461 days (4 years) with a lower bound 95% confidence interval of 812 days (2.2 years). Given the limitations in the data, an upper bound of the confidence interval is not estimable.

No ischemic strokes occurred. A total of six bleeding episodes were identified of which five episodes were minor events and one episode was classified as a major event. Table 2 displays the descriptions of the bleeding events and the INRs at which they occurred. The major bleed event identified was a retroperitoneal bleed which occurred at an INR of 2.8. Using a Cox Proportional Hazards Model, univariate correlations between risk of bleeding and baseline characteristics were examined and no statistically significant correlations were found.

DISCUSSION

The findings reported here suggest that use of warfarin for atrial fibrillation patients on hemodialysis may lead to a

Table 1. Baseline Characteristics

	VALUE (%)
Average Age (years)	77.4 ± 7
Female	12 (48)
Congestive Heart Failure	13 (52)
Hypertension	24 (96)
Diabetes	16 (64)
Use of ACEi/ARB	15 (60)
Use of β-Blocker	16 (64)
CHADS$_2$ score of 1	1 (4)
CHADS$_2$ score of 2	8 (32)
CHADS$_2$ score of 3	7 (28)
CHADS$_2$ score of ≥4	9 (36)

Figure 1. Distribution of Mean INR Measurements
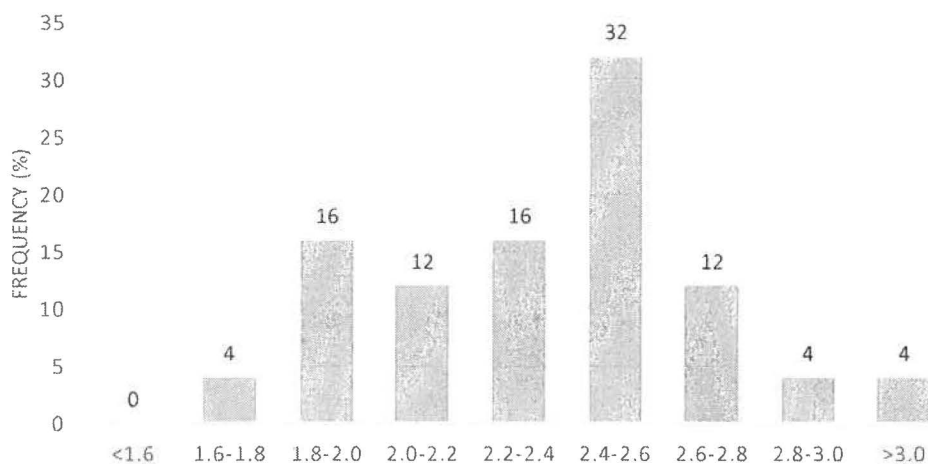
Table 2. Descriptions of Bleeding Events

EVENT NUMBER	PATIENT	SITE OF BLEED	INR PRIOR TO BLEED
1	1	Retroperitoneal bleed	2.8
2	1	Hemoptysis	3.9
3	1	Gingival bleeding	2.9
4	2	Melena	1.3
5	3	Hematuria	3.2
6	4	Hematemesis	4.6

Figure 2. Kaplan Meier Survival Curve

Time from warfarin to bleeding (days)
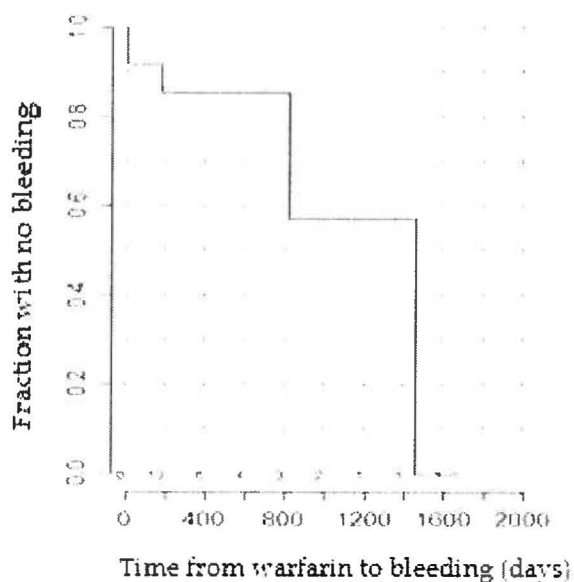
higher incidence of bleeding events despite therapeutic INRs without a decrease in risk of ischemic events. Patients had no ischemic strokes despite most patients having a higher CHADS$_2$ score of four. However, patients bled despite an average therapeutic INR of 2.4. This is an important finding as published data is limited with regards to INR reporting in relation to outcomes.

The findings from this study support previous observational studies that have reported a higher rate of bleeding events in this patient population. For instance, the systematic review and meta-analysis performed by Nochaiwong *et al* showed no statistically significant difference in all-cause mortality and thromboembolism outcomes for patients on warfarin compared to those not on it. Furthermore, they showed warfarin use was associated with a statistically higher risk of bleeding events. However, risk of hemorrhagic stroke was not increased. The studies included in this meta-analysis did not provide any data on

outcome correlation with CHADS$_2$ scores. Of greater importance, INR data which is used to assess warfarin degree of anticoagulation was not provided by Nochaiwong *et al.*[5] In a similar systematic review of stroke and bleeding outcomes of warfarin use in atrial fibrillation patients on hemodialysis, Tsai *et al* demonstrated warfarin was not associated with a decrease in rates of stroke at an expense of increased rates of bleeding. However, the data included were observational cohort studies and most did not report INR measurements.[9]

Further evidence from DOPPS showed oral anticoagulation in patients with hemodialysis increased major bleeding events, all cause and cardiovascular mortality. In addition to previous evidence, the DOPPS study was able to report moderately increased rates of bleeding and stroke events in patients on hemodialysis and using an oral anticoagulant for atrial fibrillation with high CHADS2 score (defined as ≥2), without a prior history of gastrointestinal bleed. However, DOPPS highlighted as a significant limitation the lack of INR measurements, as well as a lack of assessing warfarin adherence since patient information was collected on an outpatient basis.[6]

The rates of bleeding in patients with atrial fibrillation on hemodialysis may be higher due to other potential factors such as heparin use intra-dialysis and pathophysiological changes such as uremic platelet dysfunction.[10] There are no randomized controlled trials to show that intradialytic use of heparin increases the bleeding risk in this patient population. The data thus far is limited to case reports

showing an association rather than causation between heparin intradialysis and bleeding events.[11]

Of more importance it has been shown that there is platelet dysfunction in patients with end stage renal disease caused primarily by uremia. In patients with renal failure there is disturbance of the α-granules which contain coagulation factors V and XIII, as well as von Willebrand Factor (vWF) leading to higher bleeding propensity due to inability of platelets to bind to each other and the blood vessel wall. These patients also have impaired synthesis and release of thromboxane A_2 resulting in reduced aggregation of platelets. A higher degree of oxidative stress and inflammation can also decrease platelet function in this patient population. Arguably, these abnormalities in platelet function due to uremia toxin build up can be reversed with hemodialysis as the uremia is cleared.[10]

Therefore, irrespective of other potential confounding factors, use of warfarin in patients with atrial fibrillation and hemodialysis appears to pose an increased risk of bleeding without possibly a decreasing rate of ischemic strokes.

LIMITATIONS

The study has several limitations. First, this was a retrospective review and therefore outcome reporting was heavily reliant on complete documentation. No control group could be identified because patients with atrial fibrillation on hemodialysis that are not on warfarin were not actively tracked by pharmacists.

Finally, the study may be underpowered due to the small sample size. Also, the study duration may not have been sufficiently long to capture all possible events. All these factors may have introduced bias in the interpretation of the study results.

CONCLUSION

Patients on hemodialysis with atrial fibrillation may have a higher bleeding rate while on warfarin despite having therapeutic INRs. This may be attributed to the small sample size, duration of observation and factors such as intra-dialysis heparin use and uremic platelet dysfunction. Therefore, initiating warfarin for primary prevention in this patient population requires a careful assessment of bleeding risk factors. Further studies are warranted.

REFERENCES

1. Sood M, Komenda P, Sood AR, et al. The intersection of risk and benefit: is warfarin anticoagulation suitable for atrial fibrillation in patients on hemodialysis? *Chest.* 2009;136:1128-33.
2. Skanes A, Healey J, Cairns, J, et al. Focused 2012 Update of the Canadian Cardiovascular Society Atrial Fibrillation Guidelines: Recommendations for Stroke Prevention and Rate/Rhythm Control. *Canadian Journal Of Cardiology.* 2012;28(2):125-136.
3. Ocak G, Rookmaaker M, Algra A, et al. Chronic kidney disease and bleeding risk in patients at high cardiovascular risk: a cohort study. *Journal Of Thrombosis And Haemostasis.* 2017;16(1):65-73.

4. January C, Wann L, Alpert J, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Circulation*. 2014;130(23):e199-e267.

5. Nochaiwong S, Ruengorn C, Awiphan R, et al.Efficacy and safety of warfarin in dialysis patients with atrial fibrillation: a systematic review and meta-analysis. *Open Heart*. 2016;3(1):e000441.

6. Sood M, Larkina M, Thumma J, Tentori F, et al. Major bleeding events and risk stratification of antithrombotic agents in hemodialysis: results from the DOPPS. *Kidney International*. 2013;84(3):600-608.

7. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost*. 2005;3:692–4.

8. Kaatz S, Ahmad D, Spyropoulos C et al. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients. *J Thromb Haemost*. 2015;13:2119–26.

9. Tsai C, Marcus L, Patel P, et al. Warfarin Use in Hemodialysis Patients With Atrial Fibrillation: A Systematic Review of Stroke and Bleeding Outcomes. *Can J Kidney Health Dis*. 2017;20(4):1-13.

10. Lutz J, Menke J, Sollinger D, et al. Haemostasis in chronic kidney disease. *Nephrol Dial Transplant*. 2014;29(1):29-40.

11. Shen JI, Winkelmayer WC. Use and Safety of Unfractionated Heparin for Anticoagulation During Maintenance Hemodialysis. *Am J Kidney Dis*. 2012;60(3):473–486.