


## Hemorrhagic Versus Ischemic Risk in Patients with Atrial Fibrillation on Hemodialysis

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### Abstract

**Background:** Hemodialysis (HD) patients with atrial fibrillation (AF) have a particularly high risk of stroke and bleeding, but no high-quality evidence-based recommendations exist to properly manage these patients.

**Objectives:** We aim to evaluate the ischemic versus the hemorrhagic risk in a HD population with AF.

**Methods:** We selected incident patients that started hemodialysis between 2011 and 2015. All patients that had AF before HD, or developed AF during the follow-up, were included. Both CHA<sub>2</sub>DS<sub>2</sub>-VASC and HAS-BLED scores were calculated at the time of beginning of HD or AF diagnosis and correlated with the outcomes using a logistic regression model. The outcomes were hemorrhagic events, ischemic events and death related to any of these events. A p-value < 0.05 was set as statistically significant.

**Results:** Forty-six patients were included. Most of them had had AF before they started hemodialysis. Twenty-two patients were on oral anticoagulation (OAC). There was no significant difference between the incidence of ischemic and hemorrhagic events, regardless of the use of OAC. Previous stroke, transient ischemic attack, and thromboembolic event significantly increased the risk of an ischemic event (OR 6.78, p=0.028).

**Conclusions:** In this population, we did not observe any difference between the incidence of ischemic and hemorrhagic events, which was also true in patients with OAC. Therefore, the benefit of OAC in such patients remains questionable. However, patients with previous stroke, transient ischemic attack, or thromboembolic event seem to have a higher risk of new ischemic events and might benefit from anticoagulation.

**Keywords:** Atrial Fibrillation; Ischemic; Hemorrhage; Renal Dialysis.

### Introduction

Atrial fibrillation (AF) and chronic kidney disease (CKD) are increasingly prevalent worldwide and are associated with an increased risk of stroke, cardiovascular morbidity, and mortality.<sup>1,2</sup> Both conditions share common risk factors such as older age, hypertension and diabetes mellitus.<sup>3</sup>

The prevalence of AF is high, estimates range from 16% to 21% in CKD patients not dependent on dialysis<sup>4</sup> and 15% to 40% in patients on dialysis.<sup>5</sup> The presence of CKD in patients with AF is associated not only with an increased incidence of ischemic stroke but also with an increased risk of bleeding events. Disorders of the coagulation cascade,

activation of the fibrinolytic system, decreased platelet activity and impaired vessel wall-platelet interaction, associated with extrinsic factors, such as venous cannulation, contribute to increased risk of bleeding events in hemodialysis (HD) patients.<sup>3</sup> In a large study from Okinawa, Japan, the risk of intracerebral bleeding was tenfold higher in patients with CKD on dialysis than in those without CKD.<sup>6</sup> Gastrointestinal bleeding is also frequent and is often more severe in patients with CKD, particularly in dialysis patients.<sup>7</sup> However, despite this higher risk of ischemic and hemorrhagic events in these patients, it is not clear whether they should be anticoagulated.

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Currently, there are no randomized data on the use of vitamin K antagonists (VKAs) or direct oral anticoagulants (DOAC) in CKD patients on dialysis. Although VKAs are the most widely used, their use for stroke prevention in AF among patients on dialysis remains controversial. In CKD patients, warfarin may not promote a thromboembolic risk reduction of the same magnitude as in patients without CKD.<sup>8,9</sup> This could be explained by the difficulty in achieving therapeutic levels of the international normalized ratio (INR) in this population, due to a high interindividual variability and influences of diet, volemic status, drug metabolism, and drug-to-drug interactions.<sup>10</sup>

More recently, there has been a concern about the relationship between CKD and warfarin-induced vascular calcifications. CKD patients, especially those on dialysis, have an increased risk of medial arterial calcification. Its pathophysiology is multifactorial, but deficiencies of endogenous inhibitors of hydroxyapatite formation likely play an important role. One of these inhibitors is matrix Gla protein (MGP), a vitamin K-dependent protein synthesized by vascular smooth muscle.<sup>11</sup> Vitamin-K antagonists, such as warfarin, inhibit MGP, and may promote vascular calcification and calciphylaxis. Progression of vascular calcifications is associated with higher hemorrhagic and thromboembolic risk.<sup>12</sup>

Stroke and bleeding risk assessment tools may help in the decision-making process. Unfortunately, these tools were developed in AF patients from the general population, with various proportions of patients with mild or moderate CKD and very few or no patients on dialysis. There were some attempts to overcome this lack of data, such as the R<sub>2</sub>CHADS<sub>2</sub> (by adding two points for creatinine clearance < 60 mL/min to CHADS<sub>2</sub> to improve stroke prediction)<sup>13</sup> and ATRIA<sup>14</sup> (which contains terms for a glomerular filtration rate [GFR] < 45 mL/min/1.73 m<sup>2</sup> and proteinuria) scores. For incident dialysis patients, however, external validation studies have shown poor predictive performance of these risk scores in predicting ischemia.<sup>15,16</sup> For these reasons, CHA<sub>2</sub>DS<sub>2</sub>-VASc remains the most recommended score for risk stratification in CKD patients.<sup>17</sup>

For hemorrhagic risk, HAS-BLED score is commonly used for bleeding risk estimation in patients with AF. HAS-BLED score  $\geq 3$  indicates increased risk of oral anticoagulant-related bleeding and serves to identify high-risk patients but does not contraindicate the use of OAC. This score also had a poor predictive ability in dialysis patients.<sup>16</sup>

The aim of this study was to assess the occurrence of ischemic and hemorrhagic events in AF patients under HD, and the use of both CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED scores in this group.

## Methods

A retrospective study was carried in the outpatient HD clinic of our hospital. We selected patients that started hemodialysis in our hospital between 2011 and 2015. Only incident patients who were on regular hemodialysis treatment for at least three months were considered eligible. We included patients with previous non-valvular AF and those who developed non-valvular AF during the follow-up, which lasted until December 2019.

CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED scores were calculated and analyzed at the time of AF diagnosis or at the beginning of HD in patients with a prior diagnosis of AF.

The outcomes were hemorrhagic events that required hospitalization, ischemic events due to arterial embolism, and death related to any of these events. Anonymity was ensured, and no data that could identify the participants were recorded.

## Statistical Analysis

Statistical analysis was performed using SPSS Statistics® version 22.

Normally distributed continuous variables were expressed by means and standard deviation, whereas categorical variables were shown as frequencies and proportions. CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED scores were expressed as median and interquartile range. Differences between categorical variables were compared by the chi-squared test or the Fisher test (small samples). To correlate continuous variables, Pearson or Spearman correlation coefficients were used for normally distributed and skewed variables, respectively. To analyze the impact of each variable on the outcomes, a logistic regression was applied. A p-value < 0.05 was set as statistically significant in all analyses.

## Results

From 302 incident patients on HD, 46 (15.2 %) had AF or developed AF after HD initiation and were included in the study. There was a preponderance of the male gender (65.2%), and the mean age was 75  $\pm$  10 years old (Table 1).

**Table 1 – Study sample characterization**

Characteristics	(N=46)
Male: Female	30:16
Patients with AF prior to HD	28 (60.9%)
Age at AF diagnosis (years)	73±11.7
Age at HD initiation (years)	75±9.81
Patients with oral anticoagulation	22 (48.9%)
Follow-up (years)	3.45±2.26
Follow-up until ischemic events	2.38±1.25
Follow-up until hemorrhagic events	1.45±0.98
CHA <sub>2</sub> DS <sub>2</sub> -VASC score, median (interquartile range)	5 (4-6)
HAS-BLED score, median (interquartile range)	4 (3-4)

AF: atrial fibrillation; HD: hemodialysis.

Most of the patients (n=28; 60.9%) already had AF when they started hemodialysis, 17 (60.7%) of them were under oral anticoagulation. Of the eighteen patients that were diagnosed with AF after HD initiation, only five patients (27.8%) started anticoagulation. The most common DOAC in both situations was warfarin (21;95.5%) followed by apixaban.

The most common ischemic event during the study was embolic strokes (n=11), and there was one case of lower limb ischemia. Hemorrhagic events included five cases of gastrointestinal bleeding, three cases of cerebral hematoma and one case of abundant epistaxis. There was no significant difference between the incidence of ischemic and hemorrhagic events (p=0.219, Figure 1).

Three patients died from an ischemic event and other three died from hemorrhagic shock (Figure 2).

Oral anticoagulation did not affect the incidence of ischemic events, although there was a trend (not statistically significant) towards a higher proportion of deaths from ischemic events in patients not receiving oral anticoagulation, this difference had no statistical significance (Table 2). Considering those patients on DOAC who had an ischemic event, only four had INR within therapeutic range in that period.

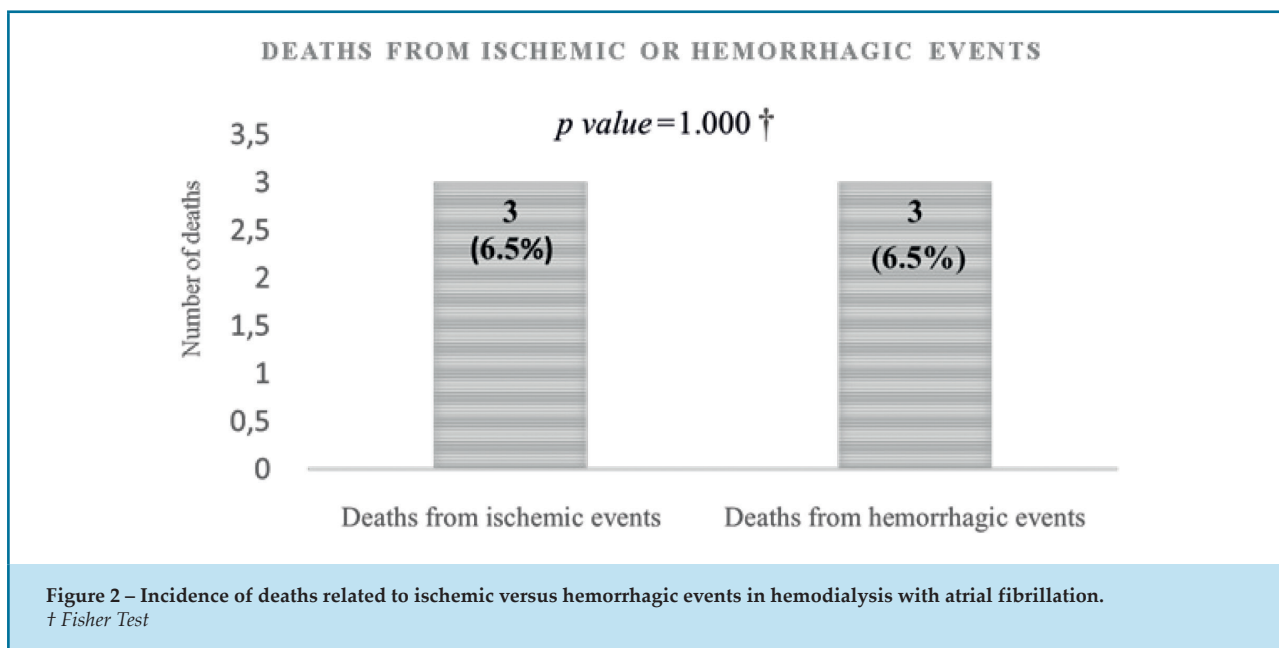
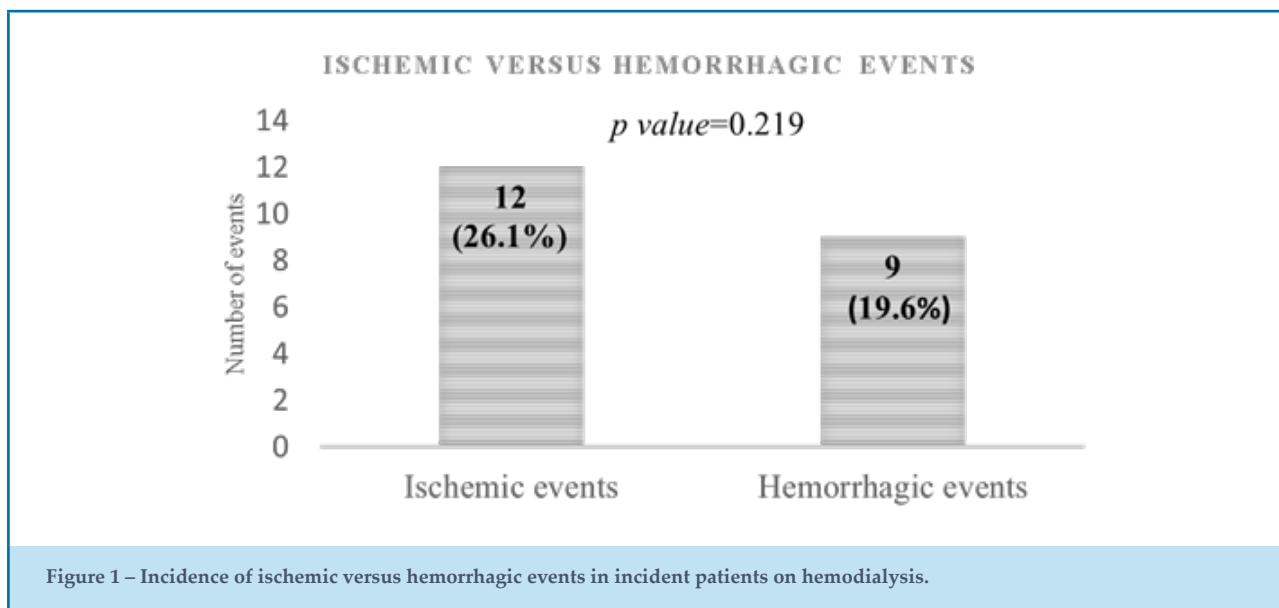
No statistical difference was found between the proportion of hemorrhagic events between patients with oral anticoagulation and patients without

anticoagulation (p=0.157). Considering the patients receiving oral anticoagulation, three patients had a supratherapeutic INR in that period (mean of 5.71±1.78).

With respect to the CHA<sub>2</sub>DS<sub>2</sub>-VASC score, median score was 5, and all patients had a high risk of stroke (minimum CHA<sub>2</sub>DS<sub>2</sub>-VASC of 2 in males). However, no statistical correlation was found between CHA<sub>2</sub>DS<sub>2</sub>-VASC score and ischemic events (p=0.396).

Considering each risk factor included in the CHA<sub>2</sub>DS<sub>2</sub>-VASC score, the odds of a new ischemic event was 6.789 times higher (p value 0.028; 95% C.I. 1.236-37.278; R2 15,6) in patients with previous stroke, transient ischemic attack (TIA) or thromboembolic event, after adjustment for oral anticoagulation, age, diabetes, vascular disease, and hypertension (Tables 3 and 4). This risk factor was not associated with an increased risk of ischemic deaths (p=0.553). No other risk factor present in CHA<sub>2</sub>DS<sub>2</sub>-VASC score (like congestive heart failure, hypertension, vascular disease history) and included in this score was significantly associated with the outcomes (Table 3).

The median HAS-BLED score was 4, and only two patients had a low risk of bleeding (HAS-BLED≤2). This score was correlated with hemorrhagic events in this population (Spearman correlation coefficient of 0.298; p=0.047). The analysis of individual risk factors of the HAS-BLED score showed no significant correlation with the incidence of hemorrhagic events (Table 5).



**Table 2 – Relationship between outcomes and oral anticoagulation in atrial fibrillation patients on hemodialysis**

	OAC	No OAC	p value
Ischemic events (n=12)	6 (33.3%)	6 (66.7%)	0.928 †
Hemorrhagic events (n=9)	6 (66.7%)	3 (33.3%)	0.157 †
Deaths from ischemic events (n=3)	0 (0.0%)	3 (100%)	0.080 †
Deaths from hemorrhagic events (n=3)	2 (66.6%)	1 (33.3%)	1.000 †

OAC: oral anticoagulation. † Fisher Test.

**Table 3 – Correlation between CHA<sub>2</sub>DS<sub>2</sub>-VASc score and ischemic events**

CHA <sub>2</sub> DS <sub>2</sub> -VASc score risk factors	All patients	Patients with ischemic events	p value
Congestive heart failure	34 (73.9%)	8 (23.5%)	0.705
Hypertension	42 (91.3%)	11 (26.1%)	1.000 †
Age ≥75 years old	27 (58.7%)	6 (22.1%)	0.524
Diabetes mellitus	26 (56.6%)	6 (23.1%)	0.524
Stroke/TIA/Thromboembolism	12 (26.1%)	6 (50.0%)	0.033*
Vascular disease	13 (28.2%)	4(30.8%)	0.721 †
Age 65-74 years old	16 (34.8%)	7 (43.8%)	0.070
Female sex	16 (34.7%)	0 (0.0%)	1.000 †

TIA: transient ischemic attack. † Fisher Test; \* p<0.05.

**Table 4 – Correlation between HAS-BLED score and hemorrhagic events in atrial fibrillation patients on hemodialysis**

HAS-BLED score risk factors	All patients	Patients with hemorrhagic events	p value
Hypertension	42 (91.3%)	9 (21.4%)	0.569 †
Abnormal liver function	1 (1.1%)	0 (0.0%)	1.000 †
Stroke	12 (26.1%)	3 (25.0%)	0.682 †
Bleeding or anemia	10 (21.7%)	3 (30.0%)	0.393 †
Labile INR	7 (15.2%)	3 (42.9%)	0.131 †
Age > 65	37 (80.4%)	9 (24.3%)	0.179†
Drugs or alcohol	13 (28.3%)	2 (15.4%)	1.000 †

INR: international normalized ratio. † Fisher Test

## Discussion

Patients with chronic kidney disease are predisposed to heart rhythm disorders, particularly AF.<sup>4,5</sup> Although treatment options for this arrhythmia are available, their use in CKD patients, especially in those under HD, is complex. Also, this population has historically been under-represented or excluded from randomized trials of treatment strategies for arrhythmias.<sup>18</sup>

Our population had an incidence of 15.2% of AF in dialysis patients, similar to the one reported in literature.<sup>5</sup>

We did not observe any difference between the incidence of hemorrhagic and ischemic events or in the

mortality from these causes in AF patients on HD, which reinforces the difficulty in assessing which patients would benefit from OAC.

Assessing the real risk of ischemic events in HD patients is very challenging not only because of limited published data, but also due to the presence of CKD-specific risk factors for stroke. Uremia, chronic malnutrition and accelerated extensive arterial calcification are associated with a high risk of ischemic events and a very high risk of death, especially among those undergoing dialysis, even in the absence of AF.<sup>3</sup> Due to epidemiological features of CKD and AF, most patients with both conditions have at least one additional risk factors for stroke and

**Table 5 - Correlation between HAS-BLED score and hemorrhagic events in atrial fibrillation patients on hemodialysis**

HAS-BLED score risk factors	All patients	Patients with hemorrhagic events	p value
Hypertension	42 (91.3%)	9 (21.4%)	0.569 †
Abnormal liver function	1 (1.1%)	0 (0.0%)	1.000 †
Stroke	12 (26.1%)	3 (25.0%)	0.682 †
Bleeding or anemia	10 (21.7%)	3 (30.0%)	0.393 †
Labile INR	7 (15.2%)	3 (42.9%)	0.131 †
Age > 65	37 (80.4%)	9 (24.3%)	0.179†
Drugs or alcohol	13 (28.3%)	2 (15.4%)	1.000 †

INR: international normalized ratio. † Fisher Test

therefore would require OAC therapy, according to their CHA<sub>2</sub>DS<sub>2</sub>-VASc score. We confirmed that in this study, in which patients had a mean CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 5 and a high risk for stroke.

In the present study, patients with AF and HD, CHA<sub>2</sub>DS<sub>2</sub>-VASc score was not correlated with the incidence of ischemic events. This data diverges from studies with a Taiwanese cohort<sup>19</sup> of OAC naive patients with AF on dialysis and an Australian cohort<sup>20</sup> of patients with AF on dialysis that reported a good correlation between ischemic stroke and CHA<sub>2</sub>DS<sub>2</sub>-VASc score. This difference could be explained by the short follow-up period and the small sample size in our study.

When we analyzed individually each risk factor of the CHA<sub>2</sub>DS<sub>2</sub>-VASc score, we found that the occurrence of previous ischemic event significantly increased the risk of another event. Since the decision to use OACs in patients with AF on dialysis must be carefully weighed against the risk of bleeding, this could be an important factor to help us selecting the patients that would benefit the most.

As discussed before, HD patients have a considerable risk of bleeding. As expected, in our study, most of the patients had a high risk of bleeding, with a HAS-BLED score  $\geq 3$ . We identified a strong correlation between this score and the occurrence of hemorrhagic events, even though the use of this score in CKD patients is not recommended by most professional society guidelines.<sup>21</sup>

Despite the high risk for ischemia and formal indication based on the CHA<sub>2</sub>DS<sub>2</sub>-VASc score, only 48.9% patients were on oral anticoagulation. Most patients had started OAC before HD induction (60.7%). This probably

reflects the difficulty regarding the decision of starting anticoagulation in dialysis patients, due to insufficient high-quality evidence to recommend OAC for prevention of ischemic events in this population.<sup>17</sup> In our study, no significant difference was observed in outcomes between patients that were on AOC and those that were not. This should be interpreted with caution since they were not under the same anticoagulant and there were no data on INR levels. Despite this, our results are in accordance with a recent meta-analysis that reviewed 15 studies with a total of 47,480 patients, and analyzed the effect of warfarin on the outcomes in end-stage renal disease patients with AF. It was found that warfarin had no effect on the incidence of ischemic stroke, risk of major bleeding or mortality.<sup>9</sup>

Our study has some limitations. First, this was an observational, retrospective study, and there is a set of variables that can interfere with the outcomes that were not controlled, such as frailty of the patients, anticoagulation during HD sessions, blood pressure control, among others. Also, both the sample size and the duration of follow-up may also have influenced the results.

However, as far as we know, this is the first time that the association between prior ischemic event and a higher risk of a new event was demonstrated in HD patients with AF. In this cohort of patients, the benefits from anticoagulation probably outweigh the risks.

We suggest that the decision of starting oral anticoagulation should consider other factors than the total CHA<sub>2</sub>DS<sub>2</sub>-VASc score, such as individual risk factors



including previous ischemic events and the hemorrhagic risk. Further clinical investigation is needed to confirm this and help in the management of this population.

## Conclusions

In this study, there was no statistically significant difference between the incidence of ischemic and hemorrhagic events in AF patients on HD, regardless of the use of oral anticoagulation. We did not find any correlation between CHA<sub>2</sub>DS<sub>2</sub>-VAsC score and ischemic events, but patients with previous stroke, TIA, or thromboembolic event seemed to have a higher risk of new ischemic events and may benefit from anticoagulation.

## Author contributions

Conception and design of the research: Sousa M, Cruz G, Silva J; acquisition of data: Sousa M, Cruz G, Vilela S, Cardoso C, Silva J; analysis and interpretation of the data: Sousa M, Bravo P, Santos JP, Santos C; statistical

analysis: Bravo P; writing of the manuscript: Sousa M, Cruz G, Vilela S, Cardoso C, Santos C; critical revision of the manuscript for intellectual content: Sousa M, Vilela S, Cardoso C, Bravo P, Santos JP, Santos C, Silva J.

## Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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## Study Association

This study is not associated with any thesis or dissertation work.

## Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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