

# Prevalence and Characteristics of Atrial Fibrillation in Turkish Patients Undergoing Hemodialysis

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## Abstract

**Objective:** Atrial fibrillation (AF) is one of the most common and cumulatively important cardiac arrhythmias. Prevalence of AF is much higher in patients with chronic kidney disease (may be up to 27%). We aimed to study the prevalence and clinical features of AF in hemodialysis centers.

**Materials and Methods:** Patients who had been under chronic in-center hemodialysis for at least 6 months and were ≥18 years of age were included in this cross-sectional study conducted at five hemodialysis centers across İstanbul between May 2017 and July 2017. Medical history, clinical (including medications and echocardiography), and laboratory data were obtained using a standardized study form.

**Results:** The data of 632 prevalent patients undergoing in-center hemodialysis (mean age 62.7±13.9 years, males 350 and females 282) were included in the analysis. AF was present in 92 (14.5%) of the patients. The prevalence of AF was lowest in patients <55 years of age and showed an increasing trend with age. While age, coronary artery disease, heart failure, and cerebrovascular events were associated with the presence of AF; left ventricular hypertrophy, diabetes and hypertension were not. Overall, 78% of patients with AF were using either single or a combination of antithrombotic agents. Less than 10% of AF patients were receiving warfarin. The rates of antiplatelet agents and warfarin use were not different between patients with a CHA2DS2-VASc score of ≥2 or less.

**Conclusion:** AF is highly prevalent in patients undergoing hemodialysis, and warfarin was used in nearly 5% of the patients with AF undergoing hemodialysis in this study, which suggests that the current knowledge is unconvincing to proceed for the treatment with anticoagulation. Further studies are needed to guide the management for prevention of strokes in patients with AF undergoing dialysis.

**Keywords:** Anticoagulation, atrial fibrillation, hemodialysis

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## INTRODUCTION

Atrial fibrillation (AF) is one of the most common and cumulatively important cardiac arrhythmias. In 2014, a Global Burden of Disease 2010 study revealed that the estimated prevalence of AF stood at 596.2 per 100,000 population in men and 373.1 in women (1). Prevalence of AF is much higher in patients with chronic kidney disease (CKD) which may be up to 27% (2). In addition to the well-known risk factors such as age, structural heart disease, hypertension, atherosclerosis, diabetes, and

hyperthyroidism which may be found both in the general and CKD populations, recent evidence has shown that obesity, obstructive sleep apnea, systemic inflammation, and electrolyte abnormalities in hemodialysis (HD) could be additional risk factors (3).

As in the general population, AF has also been found to be associated with increased risks of ischemic stroke, major bleeding, and death in end-stage renal disease (ESRD) requiring renal replacement therapies, though



there are some controversies (4, 5). However, the knowledge regarding the prevention of thromboembolic events of AF in dialysis population is weakly based on evidence. Whereas Kidney Disease: Improving Global Outcome (KDIGO) guidelines in 2011 emphasized that there is no indication for routine anticoagulation for primary prevention of stroke in ESRD patients with AF (6), the 2014 AHA/ACC/HRS guidelines presented a recommendation with an evidence level of B for warfarin treatment for the primary stroke prevention with CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 2$  and end-stage CKD (CrCl  $< 15$  mL min<sup>-1</sup>) or on hemodialysis (7).

Amid the uncertainties regarding the management of AF in patients undergoing dialysis, we aimed to study the prevalence and clinical features of AF in hemodialysis centers.

## MATERIALS AND METHODS

This was a cross-sectional study conducted at five hemodialysis centers (one home center and four satellite centers) across İstanbul between May 2017 and July 2017. All patients who had been under chronic in-center hemodialysis for at least 6 months and were  $\geq 18$  years of age were included. Only patients who declined participation in the study were excluded.

Medical history, clinical (including medications and echocardiography), and laboratory data (including urea, creatinine, sodium, potassium, calcium, phosphorus, uric acid, parathyroid hormone, hemoglobin, white blood cells, platelets, albumin, C-reactive protein, and ferritin) were obtained using a standardized study form. The diagnosis of AF was based on previous medical history and 12-lead standard electrocardiograms that were recorded within the last 3 months of data collection. CHA<sub>2</sub>DS<sub>2</sub>-VASc schema including each component as congestive heart failure, hypertension, age  $\geq 75$  years and also age 65-74 years (a separate point), diabetes mellitus, stroke, vascular disease, and sex were calculated for all cases with AF (8).

All comorbidities of patients were accepted positive as noted in their medical records and meeting the definitions as follows. Coronary artery disease was defined as a critical coronary stenosis on coronary angiography or a history of coronary intervention. Heart failure was defined as volume overload or low ejection fraction with echocardiographic findings before hemodialysis session. Cerebrovascular event was determined as thromboembolic or hemorrhagic stroke with a presence of focal or generalized neurological deficit that was proven radio-

logically. Hypertension was defined as blood pressures higher than 140/90 mm Hg before hemodialysis or taking anti-hypertensive medication. Diabetes was defined as a fasting plasma glucose level of  $\geq 126$  mg dL<sup>-1</sup>, random plasma glucose level of  $\geq 200$  mg dL<sup>-1</sup>, or using insulin and/or oral anti-diabetics. The study was conducted in accordance with the Declaration of Helsinki. Institutional ethics committee approval was not obtained due to the design of the study. Written informed consent was obtained from each subject.

## Statistical Analysis

All variables were presented as a mean  $\pm$  standard deviation. Student t-test or Mann-Whitney U test was used to compare continuous variables and chi-squared test for the comparison of categorical variables. A two-tailed p-value below 0.05 was regarded as statistically significant. Statistical analyses and graphs were performed using IBM Statistical Package for the Social Sciences software for Windows version 21.0 (IBM SPSS Corp.; Armonk, NY, USA) and GraphPad Prism 5.01 (GraphPad Software Inc., San Diego, CA, USA) software.

## RESULTS

Data of 632 prevalent patients undergoing in-center hemodialysis (mean age  $62.7 \pm 13.9$  years and M/F 350/282) were included in the analysis. The etiology of ESRD was unknown in about half of the cohort; diabetes mellitus (24%) and hypertension (16%) were most frequent causes in the remaining patients. Overall, 90% of the patients had a functional arteriovenous fistula (AVF) and the mean duration on hemodialysis was  $8.1 \pm 5$  years (Table 1).

AF was present in 92 (14.5%) patients. The prevalence of AF was lowest in patients  $< 55$  years of age and showed an increasing trend with age (Figure 1). However, there was an enormous difference in the prevalence of AF in patients with  $< 2$  years or  $\geq 2$  years duration on hemodialysis, but the duration beyond 2 years on hemodialysis did not seem to be associated with the rates of AF in a linear trend (Figure 1). Patients with AF were older ( $68.9 \pm 11.9$  vs  $61.6 \pm 13.9$ ,  $p < 0.001$ ), had higher frequencies of coronary artery disease (44% vs 22%,  $p < 0.001$ ), and heart failure (35% vs 10%,  $p < 0.001$ ) (Table 1). Hypertension was a less frequent cause of ESRD in AF patients, but the etiology was unknown in 67% of AF patients, overall. The rates of functional AVF were not different between patients with and without AF, but central venous catheters were more frequently used in AF patients although not statistically significant (12% vs 8%,  $p = 0.056$ ) (Table 1). Adequacy of hemodialysis, as measured by Kt/V, was satisfying and similar in patients with and without AF ( $1.52 \pm 0.20$  vs  $1.55 \pm 0.25$ ,  $p = 0.610$ ) (Table 1). Whereas age, coronary artery disease, heart failure, and cerebrovascular events were associated with the presence of AF, left ventricular hypertrophy, diabetes, and hypertension were not.

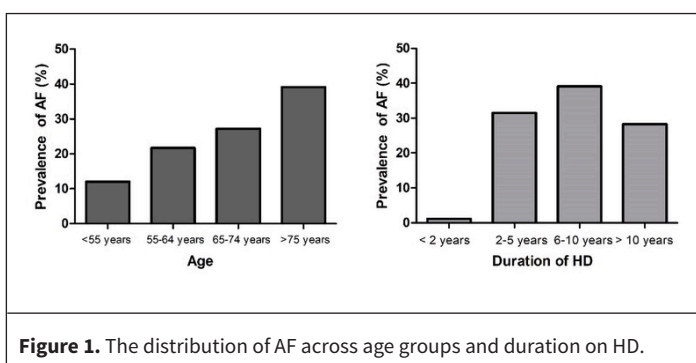
In terms of medications, patients with AF were using erythropoietin stimulating agents (ESAs) (30% vs 54%,  $p = 0.01$ ) and cal-

## Main Points

- The prevalence of atrial fibrillation in patients undergoing hemodialysis is very high as prevalence of 14.5%.
- These patients do not receive prescription specifically to prevent cardiac thromboembolic events in Turkey.
- The awareness of AF should be increased among health care professionals, patients should be screened regularly, and the treatment should be individualized with current guidelines.

**Table 1.** Clinical characteristics of all patients and the comparisons between patients with and without AF

	All Patients	AF (-)	AF (+)	p
Patients, n (%)	632 (100)	540 (85.5)	92 (14.5)	(-)
Age, mean (SD)	62.7 (13.9)	61.6 (13.9)	68.9 (11.9)	<0.001
Sex (Male), n (%)	350 (55)	297 (55)	53 (56)	0.640
Etiology of ESRD				
DM, n (%)	154 (24.4)	132 (24.4)	22 (23.9)	0.9
HT, n (%)	101 (16)	97 (18)	4 (4.4)	<0.001
GN, n (%)	24 (3.8)	24 (4.4)	0 (0)	0.03
Others, n (%)	65 (10.3)	61 (11.3)	4 (4.4)	0.04
Unknown, n (%)	288 (45.6)	226 (41.9)	62 (67.4)	<0.001
Vascular Access				
AVF, n (%)	571 (90)	490 (91)	81 (88)	0.564
AVG, n (%)	7 (1)	7 (1)	0 (0)	0.340
CVC, n (%)	54 (9)	43 (8)	11 (12)	0.056
Kt/V (Mean±SD)	1.55 (0.26)	1.55 (0.25)	1.52 (0.20)	0.610
Duration on HD (years)	8.1 (5.0)	8.0 (4.8)	9.0 (5.8)	0.123
Hypertension, n (%)	360 (57)	308 (57)	52 (56)	0.927
Diabetes, n (%)	227 (35)	195 (36)	31 (33)	0.655
Left ventricular hypertrophy, n (%)	248 (39)	211 (39)	37 (40)	0.836
Coronary artery disease, n (%)	160 (25)	119 (22)	41 (44)	<0.001
Heart Failure, n (%)	91 (14)	58 (10)	33 (35)	<0.001
Cerebrovascular disease, n (%)	98 (15)	74 (13)	24 (26)	0.002
Gastrointestinal bleeding, n (%)	29 (4)	23 (4)	6 (6)	0.338
Cancer, n (%)	16 (2)	13 (2)	3 (3)	0.630
Hepatitis B, n (%)	18 (2)	17 (3)	1 (1)	0.272
Hepatitis C, n (%)	23 (3)	20 (3)	3 (3)	0.834

**Figure 1.** The distribution of AF across age groups and duration on HD.

cium channel blockers (14.1% vs 28%,  $p=0.004$ ) less frequently, and beta blockers more frequently (Table 2). Blood tests showed no difference between groups in all parameters mentioned in the Material and Methods section.

History of cerebrovascular disease (CVD) was found in 26% of AF patients, which was significantly higher than the others (26% vs 13%,  $p=0.002$ ) (Table 1). The  $\text{CHA}_2\text{DS}_2\text{-VASc}$  score of  $\geq 2$  was found in 64 of AF patients, but the history of CVD was similar in AF patients with a  $\text{CHA}_2\text{DS}_2\text{-VASc}$  score of  $\geq 2$  or less (18/64 vs

6/28,  $p=0.543$ ) (Table 3). Overall, 78% of AF (+) patients were using either single or a combination of antithrombotic agents. The rates of antiplatelet agents and warfarin use were not different between patients with a  $\text{CHA}_2\text{DS}_2\text{-VASc}$  score of  $\geq 2$  or less (Table 3).

## DISCUSSION

In this cross-sectional, multi-centric, in-center hemodialysis study, we found some notable results. AF is highly prevalent in patients undergoing hemodialysis. Patients with AF undergoing dialysis do not receive prescription specifically to prevent cardiac thromboembolic events, but nearly 80% of AF patients were receiving at least one antithrombotic agent (mainly acetylsalicylic acid [ASA]).

CKD and AF share a number of common risk factors such as hypertension, diabetes, heart failure, atherosclerosis, and obesity (9). Therefore, the co-occurrence of these two diseases in high prevalence may not be unexpected. The overall prevalence of AF in a cross-sectional study based on medical data records of 1.9 million population was found to be 1.7% and 3% in women and men aged 65-69 years, respectively, and 3.4% and 5% in

**Table 2.** Medications that were prescribed to the patients and the comparisons between patients with and without AF

Medications	All Patients	AF (-)	AF (+)	p
Erythropoietin stimulating agents	322 (51%)	294 (54%)	28 (30%)	0.01
Acetylsalicylic acid	336 (53%)	281 (52%)	55 (59%)	0.169
Clopidogrel	25 (3%)	22 (4%)	3 (3%)	0.712
Warfarin	12 (1%)	8 (1%)	4 (4%)	0.06
Any anti-thrombotic (including combinations)	413 (65%)	341 (63%)	72 (78%)	0.005
Anticoagulation in HD				
Unfractionated heparin	129 (21%)	120 (22%)	9 (10%)	<0.001
Low molecular weight heparin	323 (51%)	293 (55%)	30 (33%)	<0.001
Without any	84 (13%)	60 (11%)	24 (26%)	<0.001
Lack of data	96 (15%)	67 (12%)	29 (31%)	<0.001
Beta-blockers	216 (34%)	145 (27%)	71 (77.2%)	<0.001
Angiotensin-converting enzyme inhibitors	51 (8%)	40 (7.4%)	11 (12%)	0.139
Angiotensin-receptor blockers	21 (3.3%)	20 (3.7%)	1 (1%)	0.196
Digoxin	6 (0.9%)	4 (0.7%)	2 (2.2%)	0.190
Ca-channel blockers	166 (26%)	153 (28%)	13 (14.1%)	0.004
Diuretics	98 (16%)	89 (16.5%)	9 (9.8%)	0.101
Alfa-blockers	32 (5%)	28 (5.2%)	4 (4.3%)	0.735

**Table 3.** Medical treatments of AF (+) patients with CHA<sub>2</sub>DS<sub>2</sub>-VASc scores of <2 vs ≥2, and the history of cerebrovascular events

	CHA <sub>2</sub> DS <sub>2</sub> -VASc <2 (n=28)	CHA <sub>2</sub> DS <sub>2</sub> -VASc ≥2 (n=64)	p
Acetylsalicylic acid	14 (50%)	41 (64%)	0.22
Clopidogrel	0	3 (4%)	0.55
Warfarin	1 (3%)	3 (4%)	0.55
Any anti-thrombotic (including combinations)	15 (53%)	57 (89%)	0.023
Anticoagulation in HD			
Unfractionated heparin	0	9	*
Low molecular weight heparin	5	25	*
Without any	7	17	*
Lack of data	16	13	*
Cerebrovascular event history	6	18	0.543

\*Lack of anti-coagulation data

women and men aged 70-74 years, respectively (10). In an intermittent mass screening study of 7173 Swedish inhabitants aged 75 to 76 years, the overall prevalence of AF was 12.3% and the intermittent ECG screening was found to increase AF detection four fold (11). In the present study, the prevalence of AF in an in-center hemodialysis population was 14.5% overall, and the rate goes up to above 30% in patients >75 years old. Although Turkish National Registry of Nephrology, Dialysis and Transplantation reported that the prevalence of AF in prevalent HD patients was only 1.33% in 2015 (12), there was a former study of 275 Turkish prevalent patients undergoing hemodialysis in which the prevalence of AF was found 10.9% (13). These findings suggest that the awareness of AF may be low in hemodial-

ysis centers because the data collection for the registry is based on the reporting system. In contrast, the exact incidence and prevalence of AF in CKD and general population may be hard to estimate because of the obstacles of having a simple and fast method to detect all forms of AF (paroxysmal, persistent, or permanent). It is clear that age is an important risk factor with regard to the prevalence of AF in hemodialysis population, and as in the general population, it multiplies the risk in an already vulnerable population (14). Although not satisfactorily studied, the underlying reasons for the high prevalence of AF in the dialysis population may not be only due to common cardiovascular risk factors, but also dialysis specific variables such as intermittent volume overload and related atrial remodeling

and fast electrolyte changes (9). The duration of hemodialysis was found similar in patients with and without AF, but when the prevalence of AF was classified according to the duration of HD, we could see that patients with less than 2 years on hemodialysis had clearly a lower rate of AF when compared with those who were undergoing hemodialysis for longer periods. In a similar study design, Genovesi et al. (15) reported that longer durations of hemodialysis were associated with higher prevalence of AF, though the main difference was seen between patients with less or more than 108 months on hemodialysis treatment. In another study where the DOPPS data were used, Wizeman et al. (14) found that the odds for AF were about 4% higher for each year of ESRD.

From a pathophysiological perspective, the presence of AF may represent a more advanced cardiovascular compromise. Therefore, the survival of patients with AF undergoing hemodialysis was consistently found to be shorter than the others in different studies (2). The design in the current study was not appropriate to investigate patient survival. Likewise, this was not an optimal setting to study the risks and incidence of strokes related to AF in hemodialysis, but we could still see that the odds for a history of CVD were two fold for patients with AF when compared with patients without AF. This is a finding in line with the solid evidence from the previous studies that the risk of stroke increased significantly with the presence of AF in ESRD patients (14, 16, 17). Furthermore, the presence of CKD seems to have an additive effect on the risk of stroke related to AF (16). If the risk of stroke or death is significantly increased with the presence of AF, then one should expect to see that AF is addressed within the prescription of hemodialysis. Nevertheless, the proportion of patients receiving warfarin for the prevention thromboembolic events does not go beyond a quarter of the total patients with CKD in the retrospective or cross-sectional studies. Similarly, less than 10% of AF patients were on warfarin in this survey. Such a practice may seem paradoxical, but the reason for this is that the risk reduction for stroke with warfarin use in patients with AF undergoing hemodialysis could not be demonstrated consistently in observational studies and meta-analyses, whereas the risk of bleeding was found significantly higher (18-20). In a more recent study, Bonde et al. (21) challenged the previous studies by the findings in their Danish registry, in which the risk of stroke was significantly lowered with the use of warfarin in CKD patients (both non-dialysis and dialysis) with high-risk AF ( $\text{CHA}_2\text{DS}_2\text{-VASc} \geq 2$ ). However, the validity of risk scores such as  $\text{CHA}_2\text{DS}_2\text{-VASc}$  and  $\text{CHADS}_2$  for AF has not still been confirmed, and as in contrast to the latter study, data from the DOPPS cohort suggest that warfarin use may be associated with an increased risk of stroke across all age groups (14). The conundrum of anticoagulation in patients with AF undergoing hemodialysis will not be resolved until well-designed randomized controlled trials are undertaken (22). More than half of all cohorts were using ASA or clopidogrel in this study. The rates of antiplatelet drug use were similar in patients with and without AF, which suggest that the indications for their use are cardio-

vascular diseases other than AF. Although less frequent than in the current study, a similar figure can be seen in the DOPPS cohort (14). The role of antiplatelet agents in the management of AF in non-CKD patients is limited, and the bleeding risks related to their use are significantly increased (23). However, unlike warfarin, the data regarding the use of antiplatelets in the stroke prevention in patients with AF undergoing hemodialysis is almost negligible.

There are important limitations in this study; this was an observational study and the associations are not necessarily causal, and the unmeasured confounders cannot be excluded. The data were collected using questionnaires, which could result in missing or incorrect data regarding the past medical history. The CVD history was reported as a whole, and it was not possible to discriminate between hemorrhagic and ischemic strokes. The diagnosis of AF was based on history and a single ECG screening, which is clearly not the optimal method for detection and classification of AF.

## CONCLUSION

AF is highly prevalent in patients undergoing hemodialysis, and effective treatment is usually not administered appropriately. A similar finding is seen in other cohorts, which suggests that the current knowledge is unconvincing and insufficient to proceed with anticoagulation treatment. Randomized controlled trials are needed to guide the management for stroke prevention in patients with AF undergoing dialysis.

**Ethics Committee Approval:** Institutional ethics committee approval was not received for this study due to the design of the study.

**Informed Consent:** Written informed consent was obtained from the patients who participated in this study.

**Author Contributions:** Concept - T.S., T.B., C.A.; Design - N.B.H., M.S., Z.A.U.; Supervision - A.Ü., T.B., E.A.; Resources - T.S., N.B.H., Y.K.; Materials - T.S., M.S., Z.A.U.; Data Collection and/or Processing - T.S., C.A., N.B.H.; Analysis and/or Interpretation - E.A., A.Ü., T.B., T.S.; Literature Search - N.B.H., Y.K.; T.S.; Writing Manuscript - N.B.H., T.S., M.S.; Critical Review - C.A., A.Ü., T.B., Z.A.U., M.S., T.S., E.A.

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