Presence of Atrial Fibrillation at the Time of Dialysis Initiation Is Associated with Mortality and Cardiovascular Events

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Key Words

Dialysis · Chronic kidney disease · Atrial fibrillation ·
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Abstract

Background: Death in dialysis patients results mainly from cardiovascular and cerebrovascular diseases. To our knowledge, no prospective study has compared the rates of mortality or cardiovascular events between patients with and without atrial fibrillation (AF) at the time of dialysis initiation. **Methods:** This study included 1,516 patients who were initiated into dialysis between October 2011 and August 2013. Rates of mortality and cardiovascular events were compared between patients with and without AF, and between AF patients with and without warfarin (WF) treatment. **Results:** The study comprised 1,025 men and 491 women with a mean age of 67.5 ± 13.1 . Of these patients, 93 had AF, while 1,423 did not; 22.6% of the former group and 9.7% of the latter group died by March 2014 ($p < 0.01$). Cardiovascular events occurred in 34.4% of patients with AF and 15.1% of patients without ($p < 0.01$). Even after adjustments for various factors, AF remained an independent risk factor for mortality (hazard ratio (HR) 1.873, 95% CI 1.168–3.002, $p < 0.01$). It was also an independent risk factor for cardiovascular events (HR 1.872, 95% CI 1.262–2.778, $p < 0.01$). No differ-

ence in any parameter was noted between the groups that did and did not receive WF treatment. **Conclusion:** Patients with AF at the time of dialysis initiation show a poor prognosis and are at high risk of cardiovascular events. Therefore, AF should be taken into consideration in dialysis patients.

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Introduction

The number of patients receiving dialysis therapy is increasing every year, and these patients show high mortality from various causes, the main ones being cardiovascular diseases and cerebrovascular diseases (CVDs) [1]. Therefore, to improve the prognosis of patients initiated into dialysis therapy, it is important to understand the characteristics of those at high risk of mortality or CVDs. On the other hand, atrial fibrillation (AF), a cause of cerebral embolism, is highly prevalent in the elderly [2, 3], and AF patients have also been reported to be at high risk for CVDs [4]. Among maintenance dialysis patients, those with AF have been reported to show a poor prognosis [5, 6].

Studies assessing the efficacy and risk of warfarin (WF) in relation to prognosis and bleeding events in patients on maintenance dialysis and patients with chronic kidney

Fig. 1. Flowchart showing the process of patient registration. We included only those patients who became stable and were able to be discharged or transferred from hospital with consent. We excluded patients who were not able to be discharged and died in hospital.

disease (CKD) have yielded conflicting results. Therefore, it remains uncertain whether WF administration is favorable for dialysis or CKD patients [7–10]. However, no prospective report has compared mortality or cardiovascular events between patients initiated into dialysis therapy with or without AF. Thus, it remains to be determined how strongly AF is associated with mortality or CVDs in patients initiated into dialysis, and dialysis-related factors also need to be examined in relation to the presence of AF. In this study, we prospectively compared mortality and the incidence of CVDs between patients with AF at the time of dialysis initiation and those without AF.

Patients and Methods

Patient Registration and Data Collection

Data from the Aichi Cohort Study of Prognosis in Patients Newly Initiated into Dialysis [11] were used in this prospective, multicenter study that included patients initiated into dialysis between October 2011 and September 2013 at 17 Japanese institutions. The study was approved by the ethics committee of the Institutional Review Board of Nagoya Daini Red Cross Hospital (IRB20110823-3) and all patients provided written informed consent. We included only those patients who became stable and were able to be discharged or transferred from hospital; patients who were not able to be discharged and died in hospital were excluded. Figure 1 is a flowchart showing the process of patient registration. Data regarding patients' background, past history, comorbidity, medicines, laboratory data, and so on, during the period of dialysis

initiation were collected. The presence of AF was confirmed by electrocardiography on the first hospital day before the initiation of dialysis. Serological data and chest X-ray were obtained at the first dialysis session, just before its initiation. Cardiac ultrasonography was performed during hospitalization. Patients were followed up until the end of March 2014.

Mortality and Cardiovascular Events

Patients were divided into 2 groups, with or without AF, and the outcomes and hazard ratios (HRs) were assessed in these groups. The primary endpoint was mortality, while the secondary endpoint was CVDs, which included coronary artery disease (CAD), heart failure, stroke, peripheral artery disease, and aortic disease (AD). CAD was defined as angiographically confirmed occlusion or stenosis of one or more coronary arteries, causing myocardial infarction or angina pectoris. Heart failure was defined as pulmonary congestion confirmed by radiograph, with hypoxemia that required hospital admission. Peripheral artery disease was defined as a disease that required admission for revascularization or amputation surgery. AD was defined as aortic aneurysm or dissection requiring surgery. The incidence of death and CVDs was investigated from survey slips that were sent to the dialysis facilities at the end of March 2014.

Administration of WF

AF patients were further divided into 2 groups: those that received WF treatment and those that did not. The incidence of death and CVDs was also investigated in these subgroups.

Statistics

Baseline characteristics were presented descriptively and tested using Student's *t* test and the χ^2 test. Survival was represented graphically using the Kaplan–Meier method and analyzed using univariate and multivariate Cox regression. HRs were represented graphically using forest plots. *p* values <0.05 were considered significant.

Results

Baseline Characteristics

The baseline characteristics of the patients are shown in table 1. The initial population included 1,524 participants, of whom 1,032 were men and 492 were women, with a mean age of 67.5 ± 13.1 . Eight patients who were untraceable were excluded. Of the remaining 1,516 patients, 93 had AF, while 1,423 did not. Patients in the AF group had a significantly higher mean age compared to those in the non-AF group (72.1 ± 10.4 vs. 67.2 ± 13.1 years, respectively; $p < 0.001$) and a significantly lower rate of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (ARB) treatment (44.8 vs. 61.1%, respectively; $p = 0.002$). The prevalence of diabetes did not differ between patients with and without AF. In addition, although the former showed a high percentage of previous underlying conditions, such as CAD, heart

Table 1. Baseline characteristics of patients with or without AF

Parameter	Patients with AF	Patients without AF	p value
Male, %	69.1	67.6	0.996
Age, years	72.1±10.4	67.2±13.1	<0.001
ACEi or ARB, %	44.8	61.1	0.002
Antiplatelet agent, %	33.0	30.2	0.573
WF, %	48.9	4.2	<0.001
β-Blocker, %	46.2	51.3	0.015
Statin, %	43.6	39.9	0.478
VDRA, %	23.4	27.3	0.414
Diabetes, %	51.1	51.1	0.996
History of CAD, %	28.7	15.0	<0.001
History of PCI, %	16.0	9.8	0.054
History of CABG, %	4.3	4.3	0.987
History of HF admission, %	39.4	19.3	<0.001
History of cerebral infarction, %	19.1	13.4	0.119
History of ICH, %	3.2	3.0	0.894
History of AD, %	10.6	5.2	0.026
History of PAD, F2, %	4.2	4.7	0.840
Amputation, %	3.2	1.5	0.225
Comorbid MI, %	8.5	5.7	0.260
Comorbid HF, %	51.1	23.8	<0.001
Comorbid PAD, %	6.4	5.0	0.551
Comorbid stroke, %	13.8	8.7	0.094
Height, cm	159.3±9.4	159.5±9.5	0.911
BMI, kg/cm ²	23.4±4.0	23.5±4.4	0.826
CTR, %	58.8±8.6	54.2±9.2	<0.001
Hemoglobin, g/dl	9.56±1.62	9.36±1.55	0.210
ALB, g/dl	3.19±0.52	3.20±0.60	0.862
eGFR, ml/min/1.7 m ²	6.34±2.79	5.39±2.17	<0.001
Na, mEq/l	137.6±4.6	137.9±4.4	0.496
K, mEq/l	4.43±0.81	4.56±0.84	0.120
cCa, mg/dl	8.72±0.95	8.61±1.06	0.303
P, mg/dl	5.97±1.73	6.39±1.89	0.038
Mg, mg/dl	2.12±0.42	2.15±0.49	0.558
ALP, U/l	263.2±99.8	264.8±176.7	0.932
LVEF, %	55.3±16.1	61.0±12.0	<0.001
Death, %	22.6	9.7	<0.001
CVD, %	34.4	15.1	<0.001

ACEi = Angiotensin-converting enzyme inhibitor; VDRA = vitamin D receptor agonist; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; PAD, F2 = peripheral arterial disease with Fontaine classification 2–4; MI = myocardial infarction; BMI = body mass index; CTR = cardiothoracic ratio; ALB = albumin; Na = sodium; K = potassium; cCa = corrected calcium; P = phosphate; Mg = magnesium; ALP = alkaline phosphatase; LVEF = left ventricular ejection fraction.

failure admission, and AD, the groups did not differ significantly in terms of the incidence of cerebral infarction or intracerebral hemorrhage (ICH). The estimated glomerular filtration rate (eGFR) [12] was significantly higher in AF patients than in non-AF patients (6.34 ± 2.79 vs. 5.39 ± 2.17 ml/min/1.7 m², respectively; $p < 0.001$).

Fig. 2. Kaplan–Meier plot of survival in patients with or without AF.

Mortality and CVDs in Patients with or without AF

The median follow-up period was 15 months. During follow-up, 159 patients died from various causes, including cardiogenic events (28 patients, 17.6%), infectious disease (28 patients, 17.6%), cancer (21 patients, 13.2%), intracranial hemorrhage (9 patients, 5.7%), peripheral artery disease (6 patients, 3.8%), cerebral infarction (3 patients, 1.9%), AD (2 patients, 1.3%), other causes (16 patients, 10.1%), and unknown causes (46 patients, 28.9%). Figure 2 shows a Kaplan–Meier plot for mortality in the groups with and without AF. The former group had a significantly higher mortality rate than the latter (22.6% (21 patients) vs. 9.7% (138 patients), respectively; $p < 0.01$; table 1). Figure 3 presents a forest plot showing the HRs of AF for death adjusted for various factors. Multivariable adjustment for cofactors showed that AF was an independent risk factor for death (HR 1.873, 95% CI 1.168–3.002, $p < 0.01$). CVDs developed in 246 patients and included CAD (82 patients, 33.3%), heart failure requiring admission (73 patients, 29.7%), cerebral infarction (29 patients, 11.8%), peripheral artery disease (19 patients, 7.7%), AD (18 patients, 7.3%), intracranial hemorrhage (15 patients, 6.1%), and others (15 patients, 6.1%). The above data include some cases of overlap. The term ‘others’ refers to cases, such as CAD or heart failure, which were difficult to diagnose precisely. A Kaplan–Meier plot for CVDs in the groups with and without AF is shown in figure 4. Consistently with the results for mortality, AF patients showed a significantly higher incidence of CVDs than those with-

Fig. 3. HRs of AF for death. Model 1 is adjusted for age and sex. Model 2 is adjusted by inclusion of administration of angiotensin-converting enzyme or ARB, diabetes, history of CAD, heart failure, and AD, and eGFR in Model 1. Model 3 is adjusted by inclusion of β -blocker administration, hemoglobin levels, corrected calcium levels, phosphate levels, and history of cerebral infarction and ICH in Model 2.

Fig. 5. HRs of AF for CVDs. Model 1 is adjusted for age and sex. Model 2 is adjusted by inclusion of administration of angiotensin-converting enzyme or ARB, diabetes, history of CAD, heart failure, and AD, hemoglobin levels, administration of antiplatelet agent, and eGFR in Model 1. Model 3 is adjusted by inclusion of β -blocker administration, corrected calcium levels, phosphate levels, and history of cerebral infarction and ICH in Model 2.

Fig. 4. Kaplan-Meier plot of CVD-free survival rate in patients with or without AF.

out AF (34.4% (32 patients) vs. 15.1% (214 patients), respectively; $p < 0.01$; table 1). Additionally, from the forest plot showing the HRs of AF for CVDs adjusted for various factors (fig. 5), it can be seen that AF was an independent risk factor for CVDs (HR 1.872, 95% CI 1.262–2.778, $p < 0.01$). Thus, patients with AF at the time of dialysis initiation had significantly higher mortality and incidence of CVDs than those without AF.

Mortality and CVDs in AF Patients with or without WF Treatment

Among the 93 patients with AF, 46 were under treatment with WF, while 47 were not. Table 2 shows the characteristics of these patient subgroups. No significant differences were observed between the groups in age, sex, or percentage of past cerebral infarction or ICH. The eGFR also showed no significant between-group differences. Importantly, mortality and the incidence of CVDs did not differ significantly between the groups with and without WF treatment (mortality: 23.9% (11 patients) vs. 21.3% (10 patients), respectively; $p = 0.761$; fig. 6) (CVDs: 32.6% (15 patients) vs. 36.2% (17 patients), respectively; $p = 0.718$; fig. 7). The CVDs included cerebral infarction and ICH. The incidence of cerebral infarction did not differ significantly between the groups with and without WF (4.3% (2 patients) in both groups; $p = 0.982$; online suppl. fig. 1, see www.karger.com/doi/10.1159/000443314). Nor did the incidence of ICH differ between the groups with and without WF in patients with AF (no patients in either subgroup).

Discussion

The results of this study showed that patients with AF at the time of dialysis initiation had significantly higher mortality and incidence of CVDs than those without AF. Thus, special attention needs to be paid to

Table 2. Baseline characteristics of AF patients with or without WF

Parameter	Patients with WF	Patients without WF	p value
Male, %	73.9	66.0	0.403
Age, years	73.6±8.5	70.7±12.1	0.184
ACEi or ARB, %	50.0	48.9	0.918
Antiplatelet agent, %	32.6	34.0	0.883
β-Blocker, %	58.7	33.3	0.014
Statin, %	50.0	50.0	0.256
VDRA, %	26.1	21.3	0.585
Diabetes, %	45.7	57.4	0.255
History of CAD, %	32.6	25.5	0.452
History of PCI, %	19.6	12.8	0.372
History of CABG, %	6.5	2.1	0.296
History of HF admission, %	43.5	36.2	0.472
History of cerebral infarction, %	23.9	14.9	0.271
History of ICH, %	6.5	0.0	0.075
History of AD, %	10.9	10.6	0.971
History of PAD, F2, %	2.2	6.4	0.317
Amputation, %	2.2	4.3	0.570
Comorbid MI, %	8.7	8.5	0.975
Comorbid HF, %	47.8	55.3	0.470
Comorbid PAD, %	2.2	10.6	0.097
Comorbid stroke, %	19.6	8.5	0.124
Height, cm	159.4±10.2	159.3±8.7	0.975
BMI, kg/cm ²	23.7±4.3	23.1±3.8	0.588
CTR, %	60.0±5.8	57.7±10.8	0.199
Hemoglobin, g/dl	9.76±1.62	9.30±1.55	0.172
ALB, g/dl	3.31±0.45	3.06±0.56	0.018
eGFR, ml/min/1.7 m ²	6.70±3.03	6.05±2.52	0.272
Na, mEq/l	137.9±4.9	137.4±4.4	0.637
K, mEq/l	4.53±0.81	4.34±0.80	0.261
cCa, mg/dl	8.72±0.90	8.78±0.98	0.760
P, mg/dl	5.41±1.69	6.44±1.59	0.004
Mg, mg/dl	2.06±0.50	2.18±0.33	0.294
ALP, U/l	248.4±113.1	277.9±85.0	0.172
LVEF, %	56.7±15.1	53.9±16.9	0.458
Death, %	23.9	21.3	0.761
CVD, %	32.6	36.2	0.718

ACEi = Angiotensin-converting enzyme inhibitor; VDRA = vitamin D receptor agonist; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; PAD, F2 = peripheral arterial disease with Fontaine classification 2–4; MI = myocardial infarction; BMI = body mass index; CTR = cardiothoracic ratio; ALB = albumin; Na = sodium; K = potassium; cCa = corrected calcium; P = phosphate; Mg = magnesium; ALP = alkaline phosphatase; LVEF = left ventricular ejection fraction.

prevent death and CVDs in these patients. We also investigated the efficacy of WF for AF patients in this population and found no differences in the rates of mortality or CVDs between patients who did or did not receive WF treatment. However, this finding could be attributable to the relatively small number of patients examined.

Fig. 6. Kaplan–Meier plot of survival in AF patients with or without WF treatment. **Fig. 7.** Kaplan–Meier plot of CVD-free survival rate in AF patients with or without WF treatment.

Previous reports showed that AF was prevalent in patients with CKD, who had a poor prognosis. Further, AF patients on maintenance dialysis were also reported to have a poor prognosis [9, 13, 14]. Additionally, there is a study similar to ours that included patients from the time of dialysis initiation and recorded mortality and CVDs [15]. Because the study revealed high rates of mortality

and CVDs at an early stage (within the first week) of dialysis initiation, their population seems to have been different from ours. Our study included only those patients who became stable and were able to be discharged or transferred from hospital. Hence, to our knowledge, no prospective report has considered the AF status of stable discharged patients from the time of dialysis initiation to determine the prognosis of AF patients. Additionally, no previous report has shown the association between the presence of AF at the time of dialysis initiation and CVDs in a population like that of this study. The main contribution of our study is that it is the first to cover these points of investigation.

Several previous studies have assessed the efficacy and risk of WF for patients with AF. Some analyzed whether WF is effective for the prevention of cerebral embolism and improving prognosis in dialysis patients, or whether it should be avoided because of the increased bleeding risk. Similarly, some studies analyzed whether or not WF is effective for preventing cerebral embolism and improving prognosis in CKD patients with AF. At present, these reports have not been able to reach a consensus on the effects of WF [3, 10, 16, 17]. Our results, too, were inconclusive as to whether WF is useful for patients with AF at the time of dialysis initiation.

We found that the rates of mortality and CVDs were twice as high in patients with AF as in those without. This could be related to the association of AF with cerebral embolism. Furthermore, the presence of AF itself suggests underlying heart problems, and patients with an underlying heart disease are inevitably susceptible to CVDs. WF was probably not efficacious in the AF patients because of the bleeding tendency in patients with renal failure [18, 19]. Although WF prevents cerebral embolism, it is associated with bleeding complications such as ICH and gastrointestinal bleeding. Unfortunately, in this study, we were not able to assess individual CVDs, such as cerebral infarction, embolism, and ICH, completely. Furthermore, the small number of patients with AF may have resulted in lack of sufficient statistical power to prove a reduced benefit or adverse effect.

Our study has some limitations. First, although we examined patients who had AF at the time of dialysis initiation, we did not ascertain whether the AF was paroxysmal or chronic. Further, we did not determine whether the AF was being treated or whether it was due to the valvular disease. There are also many cases with an unknown cause of death. This seems to have been due to patients' being transported to other hospitals for an acute disease, rather than the one in which they were usually treated.

Conclusion

Patients who have AF at the time of dialysis initiation show high rates of mortality and CVDs. Physicians should be aware of this tendency and take it into consideration when treating such patients. Further, more detailed studies are needed to refine our understanding of the relation between AF and adverse events in patients undergoing dialysis.

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Disclosure Statement

None.

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