Outcome of AF in ESRD patients

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Outcome of atrial fibrillation among patients with end-stage renal disease

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Abstract

Background. End-stage renal disease (ESRD) patients are more at risk for atrial fibrillation (AF) than the general population. However, the prognosis in ESRD patients with paroxysmal AF (PaAF), permanent AF (PAF) and paroxysmal AF transformed to permanent AF (TAF) is unknown.

Methods. In this retrospective longitudinal study, all ESRD patients with PaAF, PAF and TAF between January 2001 and December 2007 were reviewed. The develop-
ment of thromboembolic events (TEE) was analyzed using Kaplan–Meier analysis and Cox regression.

**Results.** A total of 81 patients with PaAF, 49 patients with PAF and 89 patients with TAF were reviewed. Seventy-two (32.9%) patients developed TEE, and 63 (28.8%) patients died in 36.9 ± 21.9 months. Patient survival was not significantly different between patients with different types of AF (P = 0.728). Patients with PaAF had a significantly lower TEE-free survival compared to patients with PAF (P = 0.036). In multivariate Cox regression, patients with paroxysmal AF were more at risk for TEE (P = 0.045) with a hazard ratio of 1.61 (95% confidence interval: 1.01–2.58). PaAF and congestive heart failure, hypertension, age older than 75 years, diabetes, and previous stroke or transient ischemic stroke (CHADS2) score were independently associated with an increase in TEE risk (P = 0.028 and P = 0.03).

**Conclusion.** Patient survival is not different in patients with paroxysmal and permanent atrial fibrillation. However, patients with paroxysmal AF are more at risk for the development of TEE than those with permanent AF.

**Keywords:** atrial fibrillation; ESRD; paroxysmal atrial fibrillation; permanent atrial fibrillation; thromboembolic event

**Introduction**

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice, and its incidence is increasing over the past few decades [1,2]. The prevalence of AF increases with age: 0.1% for adults <55 years, 5.8% in individuals aged between 70 and 79 years and 9% among those between 80 and 90 years [2]. AF is more prevalent in end-stage renal disease (ESRD) patients compared to age-matched individuals with normal renal function [3]. The reported prevalence of AF among ESRD patients varies between 7% and 27% [4], and the incidence was estimated to be 3.1 per 100 patient-years [5]. In addition, ESRD patients with AF had higher mortality compared to those with sinus rhythm [5,6]. Patients with AF were hospitalized more frequently than patients without AF [7] and had worse survival after hospitalization than those without AF [8]. The major complications of AF are thromboembolic events (TEE) such as stroke or transient ischemic attack. The prevalence of TEE is about 30% among chronic ESRD patients, and AF is an important risk factor [5,9].

The AF in ESRD patients has two major forms: paroxysmal atrial fibrillation (PaAF) and permanent AF (PAF). Paroxysmal AF is a short self-terminated episode of AF that may be related to dialysis treatment [4]. Permanent AF is an AF of longer duration that does not spontaneously convert to sinus rhythm. The prevalence is 3–10.9% for paroxysmal AF [10–12] and 3–23.5% for permanent AF in chronic haemodialysis (HD) patients [10–14]. In the general population, patients with PaAF had higher mortality than patients with PAF [15,16]. The re-hospitalization rate of congestive heart failure exacerbation was higher in patients with PaAF than that in PAF among patients with chronic renal failure [17]. However, the prognosis and complications for patients with paroxysmal AF and permanent AF in ESRD patients are not known. As the duration of AF is different in patients with paroxysmal and permanent AF, it is possible that survival and morbidity are different. The aim of this study is to determine survival and TEE in ESRD patients with paroxysmal and permanent AF. Patients with PaAF on the initiation of haemodialysis, which transformed to PAF during follow-up, were also included. In addition, CHADS2 score for stroke risk estimation was also taken into consideration in this study.

**Methods**

We conducted a retrospective longitudinal study and enrolled all ESRD patients (HD patients: dialyzed for >3 months, 4 h thrice weekly, using bicarbonate-based dialysate; peritoneal dialysis (PD) patients: dialyzed for >3 months using lactate-based solution) registered in China Medical University Hospital between January 2001 and December 2007. A total of 219 patients, 9.2% of entire ESRD patients, who had AF on the initiation of renal replacement therapy were identified, and the development of TEE, death, transfer to other hospital or change of renal replacement modality were followed until December 2007. In patient survival analysis, patient survival was defined as the initiation of dialysis to December 2007, date of death or the censoring events (transfer to other hospital and change of renal replacement modality); TEE-free survival was defined as the initiation of dialysis to December 2007, the development of TEE or censored by death, transfer to other hospital or change of renal replacement modality. Atrial fibrillation was defined as paroxysmal in case of spontaneous resolution of the arrhythmia and permanent when it could not be interrupted either spontaneously, by using drugs or by cardioversion [7]. Patients who had paroxysmal AF on the initiation of haemodialysis and later transformed into permanent AF were defined as TAF. Atrial fibrillation was documented by means of electrocardiographic registration. TEE was defined as the development of fatal and non-fatal cerebrovascular accident including transient ischaemic attacks (TIAs) [18]. Cerebrovascular accident was defined as the presence of focal neurological deficit requiring hospitalization, persistent for ≥24 h, which is confirmed by means of computed tomographic scan or nuclear magnetic resonance documentation of ischaemic cerebral lesions [7]. TIA was defined as neurological symptoms of vascular aetiology that resolved within 24 h [19]. CHADS2 score was used to estimate the risk of stroke [20,21]. Patient survival was defined as the initiation of renal replacement treatment to the date the patient died. TEE-free survival was defined as the initiation of renal replacement treatment to the development of fatal or non-fatal cardiovascular events including TIAs.

The biomarkers including serum haemoglobin, creatinine, albumin, potassium, total serum calcium and phosphate were recorded every month. Serum cholesterol and triglyceride were recorded every 3 months. For patients with more than two values of biomarkers available, an average value was used. Hypertension was defined as a history of hypertension (blood pressure >140/90 mmHg) for >2 years that required the initiation of antihypertensive therapy by the primary physician [22]. Diabetes mellitus was defined as a fasting glucose level of 126 mg/dl, non-fasting glucose of 200 mg/dl or a history of or treatment for diabetes [23]. A history of cardiovascular diseases (CVD), self-reported or evaluated in the medical records, included myocardial infarction, coronary artery bypass graft, percutaneous transluminal angioplasty, coronary stenosis ≥50% and ischaemic stroke at the beginning of haemodialysis [24]. Medications including aspirin, digoxin, beta blocker (atenolol, carvedilol and propanolol), calcium channel blocker (CCB, verapamil and diltiazam), amiodarone, clopidogrel and warfarin were also taken into consideration in this study. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured monthly with the patient in a supine position before HD sessions, and the 3-month average blood pressure was used for analysis.

**Statistical analysis**

Data are reported as mean ± SD or percent frequency, as appropriate. Testing for statistical significance was conducted using Student’s t test,
patients (PaAF), permanent atrial fibrillation (PAF) and PaAF transformed to PAF (TAF)

<table>
<thead>
<tr>
<th></th>
<th>PaAF n = 81</th>
<th>PAF n = 49</th>
<th>TAF n = 89</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>69.5±10.5</td>
<td>73±8.9***</td>
<td>67.5±7.6**</td>
</tr>
<tr>
<td>Male gender</td>
<td>29 (35.8)</td>
<td>21 (42.9)</td>
<td>39 (43.8)</td>
</tr>
<tr>
<td>HD</td>
<td>69 (85.2)</td>
<td>43 (87.8)</td>
<td>77 (86.5)</td>
</tr>
<tr>
<td>Mortality</td>
<td>21 (25.9)</td>
<td>14 (28.6)</td>
<td>28 (31.5)</td>
</tr>
<tr>
<td>Thromboembolic event</td>
<td>32 (39.5)*</td>
<td>11 (22.4)*</td>
<td>29 (32.6)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>32 (39.5)</td>
<td>14 (28.6)</td>
<td>36 (40.4)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>48 (59.3)*</td>
<td>25 (51)***</td>
<td>46 (51.7)**</td>
</tr>
<tr>
<td>CVD history</td>
<td>14 (17.3)**</td>
<td>5 (10.2)</td>
<td>5 (5.6)</td>
</tr>
<tr>
<td>Underlying disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CGN</td>
<td>28 (34.6)</td>
<td>15 (30.6)</td>
<td>23 (25.8)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>31 (38.3)</td>
<td>13 (26.5)</td>
<td>35 (39.3)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>17 (21)</td>
<td>14 (28.6)</td>
<td>21 (23.6)</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>16 (19.8)**</td>
<td>22 (44.9)**</td>
<td>10 (11.2)**</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>33 (40.7)**</td>
<td>16 (32.7)**</td>
<td>8 (9.0)***</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>39 (35.8)**</td>
<td>19 (38.8)**</td>
<td>4 (4.5)**</td>
</tr>
<tr>
<td>CCB</td>
<td>17 (21)**</td>
<td>24 (49)**</td>
<td>27 (30.3)**</td>
</tr>
<tr>
<td>Aspirin</td>
<td>34 (42)**</td>
<td>20 (40.8)**</td>
<td>20 (22.5)**</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>14 (17.3)**</td>
<td>1 (2.0)***</td>
<td>2 (2)***</td>
</tr>
<tr>
<td>Warfarin</td>
<td>2 (2.5)</td>
<td>5 (10.2)</td>
<td>5 (5.6)</td>
</tr>
</tbody>
</table>

HD, haemodialysis; CVD, cardiovascular disease; CCB, calcium channel blocker including verapamil and diltiazem. *Significantly different (P < 0.05) between patients with PaAF and PAF. **PAF and TAF.

**Table 2.** Clinical characteristics of patients with paroxysmal atrial fibrillation (PaAF), permanent atrial fibrillation (PAF) and PaAF transformed to PAF (TAF)

<table>
<thead>
<tr>
<th></th>
<th>PaAF n = 81</th>
<th>PAF n = 49</th>
<th>TAF n = 89</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHADS2 score</td>
<td>1.2±1</td>
<td>0.9±0.8*</td>
<td>1.5±0.7*</td>
</tr>
<tr>
<td>Pre-SBP (mmHg)</td>
<td>136±14</td>
<td>137±5</td>
<td>141±14</td>
</tr>
<tr>
<td>Pre-DP (mmHg)</td>
<td>77±8</td>
<td>79±5</td>
<td>80±7</td>
</tr>
<tr>
<td>Post-SBP (mmHg)</td>
<td>127±13</td>
<td>124±11</td>
<td>135±20</td>
</tr>
<tr>
<td>Post-DP (mmHg)</td>
<td>72±7</td>
<td>75±2</td>
<td>77±2</td>
</tr>
<tr>
<td>ΔSBP (mmHg)</td>
<td>−9±11</td>
<td>−12±10</td>
<td>−6±16</td>
</tr>
<tr>
<td>C-reactive protein (mg/dl)</td>
<td>1.6±1.5</td>
<td>0.3±0.03*</td>
<td>1.4±0.8*</td>
</tr>
<tr>
<td>Haemoglobin (mg/dl)</td>
<td>9.7±1.8</td>
<td>9.5±1.4</td>
<td>9.4±1.7</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>12±3.3</td>
<td>8.1±2.5</td>
<td>11.2±2.9</td>
</tr>
<tr>
<td>Potassium (mg/dl)</td>
<td>4.4±1.1</td>
<td>4.3±1.2</td>
<td>4.3±1.0</td>
</tr>
<tr>
<td>Albumin (mg/dl)</td>
<td>3.3±0.7</td>
<td>3.0±0.7</td>
<td>3.2±0.6</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>9.0±1.2</td>
<td>9.0±0.8</td>
<td>9.3±1.1</td>
</tr>
<tr>
<td>Phosphate (mg/dl)</td>
<td>4.9±1.8</td>
<td>5.1±1.9</td>
<td>5.1±1.8</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>180±47</td>
<td>194±37</td>
<td>200±42</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>182±160</td>
<td>219±124</td>
<td>202±133</td>
</tr>
</tbody>
</table>

PaAF, paroxysmal atrial fibrillation; PAF, permanent atrial fibrillation; TAF, paroxysmal atrial fibrillation transformed into permanent atrial fibrillation; CHADS2, CHA2DS2 score, stroke risk stratification in patients with atrial fibrillation (chronic heart failure, history of hypertension, age >75, diabetes and previous stroke or transient ischemic stroke); Pre-, predialytic; Post-, postdialytic; SBP, systolic blood pressure; DBP, diastolic blood pressure; ΔSBP, postdialytic—predialytic SBP. *Significantly different (P < 0.05) between patients with PaAF and PAF. **Haemodialysis patients.

χ² test and Mann–Whitney U test, as appropriate. One-way analysis of variance and Tukey’s post hoc test were used for the analysis of parameters between patients with PaAF, PAF and TAF. Patient survival and TEE-free survival for patients with PaAF or PAF were analyzed using Kaplan–Meier analysis with log rank test. Possible risk factors including age, sex, hypertension, diabetes, history of cardiovascular disease, diabetes, hypertension, medications, CHADS2 score, haemoglobin, C-reactive protein (CRP), albumin, creatinine, potassium, calcium, phosphate, cholesterol and triglyceride were analyzed using univariate Cox regression. Factors with a P value <0.05 were further analyzed with multivariate Cox regression. Because the duration of PAF among patients with PaAF is unknown, univariate logistic regression followed by multivariate logistic regression was used to determine possible risk factors. All calculations were carried out using a standard statistical package (SPSS for Windows, version 12, SPSS Inc., Chicago, USA).

**Results**

A total of 81 patients (37%) with PaAF, 49 (22.4%) patients with PAF and 89 (40.6%) patients with TAF were reviewed. In 36.9 ± 21.9 months follow-up, 63 (28.8%) patients died and 72 (32.9%) patients developed TEE. Demographic data of the entire study population are shown in Table 1. The mortality rate was 25.9% for patients with PaAF, 28.6% for patients with PAF and 31.5% for TAF. The chance of TEE was significantly higher among patients with PaAF (P = 0.045). Patients with TAF were significantly younger than those with PAF, and the percentage of CVD history among patients with TAF was lower than that of patients with PaAF. Moreover, 44.9% of patients with PAF took digoxin higher than that (19.8% and 11.2%) of patients with PaAF and TAF (P < 0.05); 22.5% of patients with TAF took aspirin lower than that (42% and 40.8%) of patients with PaAF and PAF (P < 0.05). The percentage of patients who took warfarin was not significantly different between patients with different types of AF.

The clinical characteristics are summarized in Table 2. The average CHADS2 score was 1.5 ± 0.7 for patients with TAF, higher than that of patients with PaAF (P < 0.05). The survival curve of patients with PaAF and PAF is shown in Figure 1. Patient survival was not significantly different between patients with PaAF and patients with TAF (P = 0.759). As shown in Figure 2, patients with PaAF had a worse TEE-free survival curve than those with PAF (P = 0.036, log rank test). In univariate Cox regression analysis, only CHADS2 score had a P value <0.05, which was introduced in multivariate Cox regression. The hazard ratio
Table 3. Hazard ratio of possible thromboembolic events risk factors in multivariate Cox regression

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHADS2</td>
<td>1.49</td>
<td>1.17–1.90</td>
<td>0.001</td>
</tr>
<tr>
<td>PaAF vs PAF</td>
<td>1.61</td>
<td>1.01–2.58</td>
<td>0.045</td>
</tr>
</tbody>
</table>

Table 4. Possible risk factors of thromboembolic events in logistic regression

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaAF</td>
<td>2.74</td>
<td>1.12–6.71</td>
<td>0.028</td>
</tr>
<tr>
<td>CHADS2</td>
<td>1.32</td>
<td>0.946–1.03</td>
<td>0.124</td>
</tr>
<tr>
<td>Age</td>
<td>0.988</td>
<td>0.946–1.03</td>
<td>0.066</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>1.16</td>
<td>0.961–1.84</td>
<td>0.124</td>
</tr>
</tbody>
</table>

PaAF, paroxysmal atrial fibrillation; PAF, permanent atrial fibrillation; CHADS2, CHADS2 score, stroke risk stratification in patients with atrial fibrillation (chronic heart failure, history of hypertension, age >75, diabetes and previous stroke or transient ischemic stroke).

Discussion

In this retrospective longitudinal study, we found that patient survival is not different between ESRD patients with paroxysmal atrial fibrillation and those with permanent atrial fibrillation. Patients with PaAF had a 60% increase in TEE risk than patients with permanent AF, and the association is independent of CHADS2 score (Table 3). Furthermore, patients with PaAF had a 2.7-fold increase in TEE risk compared to patients with PAF and TAF (Table 4). Clinical outcome for patients with PaAF transformed to PAF is rarely addressed in the literature. We found that 40.6% of patients had PaAF which later transformed into PAF upon initiation of renal replacement therapy, and 32.6% of patients with TAF developed TEE. Patient mortality of patients with TAF was not different to that of patients with PaAF nor to that of patients with PAF. The risk for TEE (32.6%) among patients with TAF was higher than that of patients with PAF (22.4%) and lower than that of patients with PaAF (39.5%). This finding may be explained by the fact that patients with TAF included patients with PaAF and PAF. Because there is no consensus in antithrombotic strategies among ESRD patients with AF [25–27], patients with PaAF tend to be treated with medication when the symptoms of PaAF developed in our clinical practice. As patients with PAF alternate between sinus rhythm and AF, it is possible that PaAF patients spend more time in arrhythmia than patients with PAF, which increases their risk for TEE [15]. Since patients with PaAF are more at risk for TEE, more interventional studies are needed to access optimal treatment in ESRD patients with PaAF.

An increasing body of evidence suggested that inflammation and oxidative stress play an essential role in the pathophysiology of atrial fibrillation [28–32]. We found that serum CRP (1.19 ± 1.0mg/dl) was higher among patients with AF than that of patients without AF (0.52 ± 0.3 mg/dl; P < 0.01), patients with TAF had higher CRP than patients with PAF (Table 2, P = 0.01) and that patients with PaAF tend to have higher CRP than patients with PAF (P = 0.08). Gedikli et al. [31] also found that patients with PaAF may have a higher CRP than other types of AF. ESRD patients with higher CRP are more at risk for stroke [33], and CRP seems to be positively associated with an increase in TEE risk in this study (Table 4).

The prevalence of AF among patients in our study is 9.2%, which is similar to the reported prevalence in previous studies [6,8,26,27]. A total of 89 patients had PaAF on the initiation of dialysis treatment which became PAF during follow-up. Because it is difficult to assure the onset of PAF in those patients, logistic regression was introduced in the analysis. Because the prevalence of AF is positively associated with duration of HD treatment [11], the prevalence of PAF may increase with longer duration of dialysis treatment.

Blood pressure changes during haemodialysis treatment can be an important prognostic factor [34,35], and episodes of arrhythmia can frequently occur after haemodialysis treatment [36–38]. However, blood pressure before and after haemodialysis treatment was not different between patients with PaAF, PAF and TAF. In logistic regression, blood
pressure was not statistically significantly associated with TEE risk. Anticoagulation treatment with warfarin in ESRD patients with chronic AF had been suggested to be a cost-effective prevention for thromboembolic stroke [27,39,40]; however, optimal stroke prevention strategies for ESRD patients remain unclear. A total of 12 (5.5%) patients took warfarin in our study; however, the use of warfarin was not associated with a decrease in TEE risk in univariate Cox regression ($P = 0.68$) and logistic regression ($P = 0.52$). Based on Wiesholzer's study [18], an annual risk of stroke in HD patients was 1%, and AF is not a risk factor for stroke. Similarly, our previous study also showed a relatively lower risk for stroke among Chinese HD patients [33]. This finding may be explained either by the low percentage of warfarin treatment in our study or the low incidence of stroke among HD patients.

The retrospective design, mix of patients treated with hemodialysis and peritoneal dialysis, no official certificate for the presence of arrhythmia, undefined nature of stroke such as haemorrhagic or ischaemic stroke and the lower percentage of warfarin treatment are potential limitations of this study. HD patients may have a different TEE risk compared to PD patients because of heparin treatment in haemodialysis sessions. More studies are needed to determine if TEE risk is different between HD and PD patients and if warfarin prevention among Chinese ESRD patients is effective.

In conclusion, ESRD patients with paroxysmal atrial fibrillation had similar survival to patients with permanent atrial fibrillation. The risk for TEE is significantly higher among patients with paroxysmal atrial fibrillation than those with permanent atrial fibrillation.

References

High-flux or low-flux dialysis: a position statement following publication of the Membrane Permeability Outcome study

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Keywords: dialysis; ERBP; flux; MPO study; survival

Aim and scope

The European Renal Best Practice (ERBP) Advisory Board recently decided to follow up existing guidelines, and to publish position statements when new evidence would necessitate a change in the existing guideline [1]. The purpose of this document is to provide guidance on the interpretation and relevancy of the current European Best Practice Guideline (EBPG) on dialysis strategy [2], in the light of the recently published Membrane Permeability Outcome (MPO) study [3]. This position statement is intended to be considered in conjunction with the current guideline. It does not replace the guideline as we do not include a new systematic review of the literature. The MPO study specifically focused on the question whether the use of a high-, compared to a low-flux dialyser membrane, would have a measurable effect on survival.

Current guideline

The current European guideline relating to dialyser membrane permeability or flux is contained in the EBPG guideline on dialysis strategies [2], published in 2007. This document contains the following recommendation:

Guideline 2.1: The use of synthetic high-flux membranes should be considered to delay long-term complications of haemodialysis therapy. Specific indications include: to reduce dialysis-related amyloidosis (level III); to improve control of hyperphosphataemia (level II); to reduce the increased cardiovascular risk (level II); to improve control of anaemia (level III).

At the time the guideline was prepared, there was insufficient evidence available to link membrane permeability with survival. This lack of evidence is reflected in the wording of the guideline, which mentions only relatively soft or surrogate outcomes such as anaemia, hyperphosphataemia, etc. The evidence for improved phosphate control is controversial. The wording ‘should be considered’, is, in effect, a level II (weak) recommendation. The evidence regarding the outcomes are moderate or weak (levels II or III) according to the grading system used in the guideline.

The guideline cites the Hemodialysis (HEMO) study [4] as the only randomized clinical trial (RCT) available which addressed the influence of high-flux dialysis on survival directly. This study found no difference in survival between high- and low-flux in the study group as a whole. However, post hoc, subgroup analysis suggested that high-flux dialy-