Hazards of antithrombotic therapy on hemodialysis patients with atrial fibrillation and high thromboembolic risk: a Taiwanese population-based cohort study

Yu-Hsien Lai¹, Tsung-Cheng Hsieh², Chu-Lin Chou³, Chiu-Huang Kuo¹, Yu-Li Lin¹, Chih-Hsien Wang¹, Te-Chao Fang⁴,⁵

¹Division of Nephrology, Department of Internal Medicine, Hualien Buddhist Tzu Chi General Hospital, Hualien, Taiwan; ²Institute of Medical Sciences, Tzu Chi University, Hualien, Taiwan; ³Division of Nephrology, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan; ⁴Division of Nephrology, Department of Internal Medicine, Taipei Medical University Hospital, Taipei Medical University, Taipei, Taiwan; ⁵Division of Nephrology, Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan

Received March 20, 2017; Accepted August 9, 2017; Epub September 15, 2017; Published September 30, 2017

Abstract: The benefit of antithrombotic therapy in hemodialysis (HD) patients with atrial fibrillation (AF) and high thromboembolic risk has not been proved. The purpose of this study was to examine the effects of antithrombotic therapy on HD patients with AF and high thromboembolic risk. We analysed the outcomes of 1,197 HD patients with AF having CHA₂DS₂-VASc scores ≥ 2 points by using data retrieved from the National Health Insurance Research Database between 1997 and 2008. Four groups of patients, namely aspirin, warfarin, aspirin combined with warfarin, and non-treatment groups, were compared. Between the treatment and non-treatment groups, multivariate Cox proportional analysis revealed no significant difference in the mortality. Among the treatment groups, the aspirin combined with warfarin group had a higher mortality than that of the aspirin group. No significant differences were observed among the four groups in the risks of haemorrhagic stroke, gastrointestinal bleeding, congestive heart failure, acute coronary syndrome, and peripheral arterial occlusive disease. However, the risk of ischemic stroke was significantly higher in the aspirin and the aspirin combined with warfarin groups than in the non-treatment group. In HD patients with AF and with high thromboembolic risks, the mortality rate was not significantly different between treatment groups and non-treatment group. However, the risk of ischemic stroke was significantly higher in aspirin and aspirin plus warfarin groups when compared with non-treatment group. Therefore, the usage of aspirin and warfarin in these patients should be meticulously evaluated.

Keywords: Atrial fibrillation, hemodialysis, anticoagulation therapy, aspirin, warfarin

Introduction

Atrial fibrillation (AF) is a common arrhythmia characterized by abnormal atrial activity, and it is associated with increased morbidity and mortality rates secondary to embolism formation in the general population. The CHA₂DS₂-VASc score is used for stratifying stroke risk in patients with AF, and greater stroke risk is observed in those with a higher score [1]. Current guidelines recommend implementing optimal management with antiplatelets or anticoagulants based on the CHA₂DS₂-VASc score to reduce the mortality rate and stroke in the general population [2].

The prevalence of AF in patients with chronic kidney disease (CKD) determined in the Chronic Renal Insufficiency Cohort (CRIC) study was approximately 2.5-3 times higher than that in the general population [3]. Moreover, the Dialysis Outcomes and Practice Patterns Study (DOPPS) conducted during 1996-2004 revealed a markedly increased prevalence of AF for all age groups in patients with end stage renal disease (ESRD) [4]. In addition, the United States
Antithrombotic therapy on HD patients with AF and high thromboembolic risk

Renal Data System (USRDS) (www.USRDS.org) had shown 13-fold increase of AF prevalence in hemodialysis (HD) patients and a 5-year mortality rate as high as 80% [5, 6]. The pathophysiological changes in renal insufficiency result in both hypo and hyper coagulopathy [7]. However, the subjects in studies related to AF management strategies were excluded not only ESRD patients on dialysis but also CKD patients. Despite the recommendation of antithrombotic therapy based on the CHA2DS2-VASc score in the general population, studies have suggested that the benefit of anticoagulant use should be carefully evaluated in HD patients with AF [8, 9]. For example, a previous study revealed that warfarin can reduce the risk of ischemic stroke and death compared with aspirin in the Chinese general population with non-valvular AF [10]. By contrast, one recent study demonstrated that warfarin usage did not reduce the risk of ischemic stroke in dialysis patients with AF [11]. Although HD patients have increased bleeding risks compared with the general population, no consensus from current guidelines is available on the use of aspirin or warfarin in HD patients. Moreover, examining the benefits of antithrombotic therapy on HD patients with AF and high thromboembolic risk is crucial. The purpose of this study was to evaluate the effects of antithrombotic therapy on HD patients with AF and high thromboembolic risk.

Materials and methods

Database

Our data were obtained from the health insurance database provided by the Taiwan National Health Research Institutes (NHRI). The NHRI maintains the National Health Insurance Research Database (NHIRD), which provides data for longitudinal cohort studies [12, 13]. Since 1995, the Taiwan National Health Insurance (NHI) program, a compulsory social insurance program, was launched in Taiwan to provide healthcare services to Taiwan residents. As of 2007, more than 99% of Taiwan residents were enrolled in the NHI program. The database of this program contains registration files and original claims data for reimbursement, and these data are encoded by the NHRI to ensure privacy.

In the NHI system, certain major diseases such as ESRD are classified as ‘catastrophic illnesses’. To obtain catastrophic illness certification, applicants are formally reviewed according to guidelines and regulations. Once the certification is issued, relevant information is entered into the catastrophic illness certificate of the patients. These patients are not required to pay deductibles for care for the illness or its related conditions during the validity period of the certificate. In our study, we used a longitudinal health insurance database for people with catastrophic illnesses provided by the NHRI. The database provides information on all chronological applications and transitional data from the catastrophic illness certificate, including outpatient and inpatient claims data during 1995-2008 and death dates for the deceased patients.

Study cohort and patient selection

To protect privacy, the individuals’ identifications are encrypted within the NHI database. This study was exempted from review by the Ethics Committee and Human Subjects Institutional Review Board of Tzu Chi Hospital, Hualien, Taiwan (TCH IRB Number: 101-126). All methods were performed in accordance with the relevant guidelines and regulations by Tzu Chi Hospital, Hualien. We obtained NHI catastrophic illness registry files for all patients for the period of 1 January 1997 to 31 December 2008 to construct our study population. We included patients who were newly diagnosed with ESRD [International Classification of Diseases (ICD-9) code 585], free of cancer, and receiving hemodialysis for > 3 months. Moreover, only data from 105, 956 patients who received their first ESRD certification during 1997-2008 from the longitudinal catastrophic illness database were included to ensure the identity of the ESRD patients (ICD-9 code 585). Exclusion criteria were duration of HD lasting < 3 months; diagnosis with cancer before catastrophic illness certification for ESRD; receipt of renal transplantation either before or after dialysis; and receipt of peritoneal dialysis.

Among the identified ESRD patients, HD patients without a diagnosis code for AF (ICD-9: 427.31) were excluded from our study. The CHA2DS2-VASc score was then calculated for HD patients with a diagnosis of AF. We conducted subgroup analyses of patients with a CHA2DS2-VASc score ≥ 2, who represented patients with high thromboembolic risk. Four
Antithrombotic therapy on HD patients with AF and high thromboembolic risk

Figure 1. Identification of hemodialysis patients with atrial fibrillation and high thromboembolic risk. N: number of events.

Cohort characteristics

Initially, we identified 105,956 ESRD patients on dialysis. Patients who had cancer, were on peritoneal dialysis, underwent HD for < 3 months, or received renal transplantation were excluded first; subsequently, patients without AF were excluded. Finally, 1,503 patients on HD with an AF diagnosis remained. Among these patients, 1,197 with a CHA₂DS₂-VASc score ≥ 2 were included in our study (Figure 1).

The characteristics of the four groups of patients (aspirin, warfarin, aspirin combined with warfarin, and non-treatment) are listed in Table 1. The overall mean follow-up time was 54.6 ± 30.5 months. Significant differences in patient demography among the four groups were observed in sex, age, and hypertension. Among the four groups, more female and elderly patients were in the non-treatment group, whereas male patients, younger patients, and those with hypertension comprised a larger proportion in the aspirin combined with warfarin group. No significant difference was observed in other comorbidities.

Cox proportional hazards analysis of mortality

Table 2 shows the results of a multivariate Cox proportional hazards analysis for outcomes of AF in HD patients with high thromboembolic risk. The multivariate Cox proportional analysis revealed no significant difference in the total mortality rate between the treatment groups (aspirin, warfarin, and aspirin combined with warfarin) and the non-treatment group (Figure 2). However, the aspirin combined with warfarin group had a higher total mortality rate than that of the aspirin group (HR: 1.47, \(P < 0.001\)) (Figure 2). Moreover, the total mortality rate was independently higher in elderly patients than in patients aged ≤ 64 years (HR: 1.30, \(P = 0.042\) for those aged 65-74 years; HR: 2.17, \(P < 0.001\) for those aged ≥ 75 years). Moreover, it was higher in male (HR: 1.21, \(P = 0.042\)) and diabetic patients (HR: 1.33, \(P = 0.002\)), whereas patients with hyperlipidemia had a lower
Antithrombotic therapy on HD patients with AF and high thromboembolic risk

**Table 1. Characteristics of atrial fibrillation in hemodialysis patients with high thromboembolic risk**

<table>
<thead>
<tr>
<th></th>
<th>Aspirin N (%)</th>
<th>Warfarin N (%)</th>
<th>Aspirin+ Warfarin N (%)</th>
<th>Non-treatment N (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex (Male)</strong></td>
<td>327 (40.2)</td>
<td>11 (35.5)</td>
<td>94 (43.7)</td>
<td>34 (24.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>≤ 64</td>
<td>260 (31.9)</td>
<td>7 (22.6)</td>
<td>91 (42.3)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>65-74</td>
<td>318 (39.1)</td>
<td>9 (29.0)</td>
<td>79 (36.7)</td>
<td>53 (38.7)</td>
<td></td>
</tr>
<tr>
<td>≥ 75</td>
<td>236 (29.0)</td>
<td>15 (48.4)</td>
<td>45 (20.9)</td>
<td>84 (61.3)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>371 (45.6)</td>
<td>13 (41.9)</td>
<td>102 (47.4)</td>
<td>51 (37.2)</td>
<td>0.253</td>
</tr>
<tr>
<td>Hypertension</td>
<td>727 (89.3)</td>
<td>27 (87.1)</td>
<td>201 (93.5)</td>
<td>114 (83.2)</td>
<td>0.022</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>252 (31.0)</td>
<td>9 (29.0)</td>
<td>77 (35.8)</td>
<td>38 (27.7)</td>
<td>0.413</td>
</tr>
</tbody>
</table>

N, number of cases.

**Table 2. Cox proportional hazards model for outcome events of atrial fibrillation in hemodialysis patients with high thromboembolic risk**

<table>
<thead>
<tr>
<th></th>
<th>Aspirin N (%)</th>
<th>Warfarin N (%)</th>
<th>Aspirin+ Warfarin N (%)</th>
<th>Non-treatment N (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>321 (39.4)</td>
<td>14 (45.2)</td>
<td>89 (41.4)</td>
<td>60 (43.8)</td>
<td>0.718</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>30 (3.7)</td>
<td>1 (3.2)</td>
<td>7 (3.3)</td>
<td>2 (1.5)</td>
<td>0.599</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>119 (14.6)</td>
<td>3 (9.7)</td>
<td>31 (14.4)</td>
<td>10 (7.3)</td>
<td>0.111</td>
</tr>
<tr>
<td>CHF</td>
<td>341 (41.9)</td>
<td>14 (45.2)</td>
<td>83 (38.6)</td>
<td>39 (28.5)</td>
<td>0.024</td>
</tr>
<tr>
<td>ACS</td>
<td>59 (7.2)</td>
<td>0 (0)</td>
<td>15 (7.0)</td>
<td>0 (0)</td>
<td>0.006</td>
</tr>
<tr>
<td>PAOD</td>
<td>116 (14.3)</td>
<td>4 (12.9)</td>
<td>30 (14.0)</td>
<td>10 (7.3)</td>
<td>0.169</td>
</tr>
<tr>
<td>GI bleeding</td>
<td>331 (40.7)</td>
<td>14 (45.2)</td>
<td>77 (35.8)</td>
<td>48 (35.0)</td>
<td>0.352</td>
</tr>
</tbody>
</table>

CHF, Congestive heart failure; ACS, acute coronary syndrome; PAOD, peripheral arterial occlusive disease; GI, gastrointestinal.

**Figure 2.** Adjusted survival probability of atrial fibrillation in hemodialysis patients with high thromboembolic risk in the Cox regression model. A+W: aspirin combined with warfarin.

**Discussion**

This nationwide cohort study was the first to evaluate the effects of antithrombotic therapy on HD patients with AF and high thromboembolic risk. The major findings of our study, obtained after multivariate adjustment, are summarized as follows: (1) the mortality rate was not significantly different between the treatment (aspirin, warfarin, and aspirin combined with warfarin) and non-treatment groups; however, the aspirin combined with warfarin group had a higher mortality rate than the aspirin group; (2) the risk of ischemic stroke was significantly higher in the aspirin and aspirin combined with warfarin groups than in the non-treatment group; (3) adverse outcomes, including hemorrhagic stroke, gastrointestinal bleeding, congestive heart disease, acute coronary syndrome, and peripheral arterial occlusive disease, were not significantly different between the treatment groups (aspirin, warfarin, and aspirin combined with warfarin) and the non-treatment group.

In our study, no significant difference was observed in the total mortality rate between the group (HR: 2.01, P = 0.039) and the aspirin combined with warfarin group (HR: 2.46, P = 0.016) than in the non-treatment group (Figure 3A). Moreover, the risk of ischemic stroke was independently higher in elderly patients (HR: 1.72, P = 0.008 for those aged 65-74 years; HR: 1.80, P = 0.010 for those aged ≥ 75 years; Table 4). However, no significant differences in risk were observed among the four groups in hemorrhagic stroke (Figure 3B), congestive heart failure, gastrointestinal bleeding, peripheral arterial occlusive disease, and acute coronary syndrome (Figure 4).

**Adverse outcomes**

Regarding adverse outcomes, the risk of ischemic stroke was higher in the aspirin group (HR: 2.01, P = 0.039) and the aspirin combined with warfarin group (HR: 2.46, P = 0.016) than in the non-treatment group (Figure 3A). Moreover, the risk of ischemic stroke was independently higher in elderly patients (HR: 1.72, P = 0.008 for those aged 65-74 years; HR: 1.80, P = 0.010 for those aged ≥ 75 years; Table 4). However, no significant differences in risk were observed among the four groups in hemorrhagic stroke (Figure 3B), congestive heart failure, gastrointestinal bleeding, peripheral arterial occlusive disease, and acute coronary syndrome (Figure 4).
Table 3. Adjusted hazard ratios for total mortality in hemodialysis patients with atrial fibrillation and high thromboembolic risk

<table>
<thead>
<tr>
<th>Treatment vs. Non-treatment groups</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin vs. None</td>
<td>0.84</td>
<td>0.63-1.12</td>
<td>0.234</td>
</tr>
<tr>
<td>Warfarin vs. None</td>
<td>1.07</td>
<td>0.60-1.93</td>
<td>0.821</td>
</tr>
<tr>
<td>A+W vs. None</td>
<td>1.23</td>
<td>0.88-1.73</td>
<td>0.227</td>
</tr>
</tbody>
</table>

Comparison between treatment groups

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin vs. Warfarin</td>
<td>0.90</td>
<td>0.53-1.51</td>
<td>0.683</td>
</tr>
<tr>
<td>A+W vs. Aspirin</td>
<td>1.47</td>
<td>1.16-1.86</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>A+W vs. Warfarin</td>
<td>1.15</td>
<td>0.65-2.04</td>
<td>0.204</td>
</tr>
</tbody>
</table>

Sex (Male) 1.21 1.01-1.46 0.042
Age, years
<64 Reference
65-74 1.30 1.01-1.67 0.042
≥ 75 2.17 1.69-2.80 < 0.001
Diabetes mellitus 1.33 1.11-1.60 0.002
Hypertension 1.03 0.76-1.38 0.869
Hyperlipidaemia 0.80 0.65-0.98 0.035

A+W, aspirin combined with warfarin; HR, hazard ratio; CI, confidence interval.

Figure 3. Probability of freedom from stroke in hemodialysis patients with atrial fibrillation and high thromboembolic risk in the Cox regression model. A. Ischemic stroke. B. Haemorrhagic stroke. A+W: aspirin combined with warfarin.

Antithrombotic therapy on HD patients with AF and high thromboembolic risk

result was similar to that of previous studies. One cohort study on 1,671 HD patients with AF comparing a warfarin group with a non-treatment group demonstrated no difference in the all-cause mortality rate [8]. In addition, a multicentre randomized trial investigated whether warfarin was superior to aspirin in preventing thromboembolism in the Chinese general population with non-valvular AF. The study revealed no difference in the mortality rate between the warfarin and aspirin groups (1.2% vs. 2.2%, P = 0.33) [10].

Age, diabetes mellitus, and hyperlipidaemia were independent risk factors for total mortality in this study. Moreover, a previous study revealed that age was an independent risk factor for total mortality in HD patients with AF [4]. Diabetes mellitus was considered an independent risk factor because patients with diabetes mellitus exhibit abnormalities in platelet functions, such as platelet aggregation, coagulation, and fibrinolysis, possibly resulting in thrombus formation and increased thromboembolic risk [14]. Regarding hyperlipidaemia, our results revealed an inverse relationship between the cholesterol level and mortality rate, which is compatible with the findings of previous studies, which revealed a reverse epidemiologic phenomenon for hypercholesterolemia in HD patients [15]. Studies have shown that statin therapies for hypercholesterolemia, such as 4-D, AURORA, and SHARP, effectively reduces the cholesterol level in HD patients; however, a lower cholesterol level does not result in decreased mortality or cardiovascular outcomes [16-18].

Our results revealed that aspirin did not reduce the risk of ischemic stroke in HD patients with AF compared with the non-treatment group, and it even increased the risk of ischemic stroke in this population. One cohort study, which included 1,671 HD patients with pre-existing AF, revealed that no significant reduction in the risk of new ischemic stroke between aspirin treatment and non-treatment groups (95% CI: 0.58-1.63) [8]. Another cohort study revealed no significant differences between
### Table 4. Adjusted hazard ratios for ischemic stroke in hemodialysis patients with atrial fibrillation and high thromboembolic risk

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment vs. Non-treatment groups</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin vs. None</td>
<td>2.01</td>
<td>1.04-3.88</td>
<td>0.039</td>
</tr>
<tr>
<td>Warfarin vs. None</td>
<td>1.48</td>
<td>0.41-5.43</td>
<td>0.551</td>
</tr>
<tr>
<td>A+W vs. None</td>
<td>2.46</td>
<td>1.18-5.10</td>
<td>0.016</td>
</tr>
<tr>
<td>Comparison between treatment groups</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin vs. Warfarin</td>
<td>1.58</td>
<td>0.50-4.98</td>
<td>0.438</td>
</tr>
<tr>
<td>A+W vs. Aspirin</td>
<td>1.22</td>
<td>0.82-1.82</td>
<td>0.249</td>
</tr>
<tr>
<td>A+W vs. Warfarin</td>
<td>1.66</td>
<td>0.50-5.46</td>
<td>0.408</td>
</tr>
<tr>
<td>Sex (Male)</td>
<td>0.97</td>
<td>0.70-1.35</td>
<td>0.850</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 64</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65-74</td>
<td>1.72</td>
<td>1.15-2.56</td>
<td>0.008</td>
</tr>
<tr>
<td>≥ 75</td>
<td>1.80</td>
<td>1.15-2.80</td>
<td>0.010</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.31</td>
<td>0.95-1.80</td>
<td>0.098</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.44</td>
<td>0.79-2.62</td>
<td>0.235</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>1.01</td>
<td>0.72-1.42</td>
<td>0.947</td>
</tr>
</tbody>
</table>

A+W, aspirin combined with warfarin; HR, hazard ratio; CI, confidence interval.

Aspirin and non-treatment groups (HR: 0.88, P = 0.54) [19] in the risk of ischemic stroke in 153 patients with non-valvular AF on renal replacement therapy. The association of increased ischemic stroke with aspirin usage is not clearly understood, possibly because aspirin is predominantly excreted by the kidneys as salicylic acid, increasing platelet adhesion and reducing 13-hydroxyoctadecadienoic acid production [20]. The excretion of the metabolite (salicylic acid) of aspirin is impaired in HD patients, and this accumulation of salicylic acid can cause adverse side effects. The effect of aspirin is based on a balance between thromboxane and prostacyclin; prostacyclin reduces thrombosis by inhibiting platelet aggregation, whereas thromboxane leads to thrombosis. Low-dose aspirin usage can selectively inhibit thromboxane production; however, high-dose aspirin usage inhibits both platelet aggregation and vascular synthesis of the antiaggregatory vasodilator prostaglandin I2 (PGI2), which leads to thrombogenesis [21]. This phenomenon has been postulated to be related to the inhibited synthesis of endothelial derived prostacyclin, which results in increased platelet adhesiveness [22, 23]. Another reason could be ‘aspirin resistance’ among various ethnicities [24]. Various genetic polymorphisms may cause resistance to the antithrombotic effects of aspirin. Moreover, one study revealed an increased incidence of left atrial appendage thrombosis in HD patients receiving aspirin, which may contribute to the higher incidence of ischemic stroke [14]. Current studies on aspirin usage for cardiovascular disease mostly exclude patients with eGFR (estimated glomerular filtration rate) < 10 [25].

Our results revealed that warfarin usage exhibited no benefit in the prevention of ischemic stroke compared with no treatment and the other treatments in HD patients with AF and high thromboembolic risk. Previous studies have established no definitive conclusion regarding the effect of warfarin in the prevention of ischemic stroke in HD patients with AF. For example, a cohort study revealed that the occurrence of ischemic stroke in elderly HD patients (aged > 65 years) with AF was similar (95% CI: 0.61-1.70) between warfarin users (237 patients) and nonusers (948 patients) [26]. However, another cohort study revealed that warfarin therapy increased the risk of new ischemic stroke (95% CI: 1.29-2.90) in HD patients with pre-existing AF in a population with mixed races compared with nonusers [8]. Altogether, age and race may be the significant factors contributing to these conflicting results. Differences in thromboembolic risk were observed among various races, and a higher risk of warfarin-related intracranial haemorrhage was observed among Asian patients with AF compared with Caucasians in the general population [27]. Therefore, the usage and appropriate dosage of warfarin in Asians may differ from those in Caucasians [28]. Another factor may be that anticoagulants are underused in Asians [27, 29]. Anticoagulant underuse might be a reason for our study demonstrating no benefit of warfarin usage in preventing ischemic stroke in HD patients with AF and high thromboembolic risk.

Regarding the concurrent usage of aspirin combined with warfarin, our results revealed that the aspirin combined with warfarin group had a significantly higher total mortality rate than that
Antithrombotic therapy on HD patients with AF and high thromboembolic risk

![Figure 4](image)

Figure 4. Adjusted hazard ratio (HR) and 95% confidence interval (CI) of outcome events of atrial fibrillation in hemodialysis patients with high thromboembolic risk. A, aspirin; W, warfarin; A+W, aspirin combined with warfarin; GI, gastrointestinal; CHF, congestive heart failure; PAOD, peripheral arterial occlusive disease; ACS, acute coronary syndrome.

of the aspirin group (HR: 1.47, \(P < 0.001\)); however, the total mortality rate of the aspirin combined with warfarin group was not significantly different from that of the non-treatment (HR: 1.23, \(P = 0.227\)) and warfarin groups (HR: 1.15, \(P = 0.204\)). In addition, the aspirin combined with warfarin group had an increased risk of ischemic stroke (HR: 2.46, \(P = 0.016\)) compared with the non-treatment group. A small cohort study involving 45 AF patients who underwent renal replacement therapy and received aspirin combined with warfarin treatment showed no benefit in lowering the risk of ischemic stroke or thromboembolism compared with that in a non-treatment group (HR: 0.82, \(P = 0.62\)) [19]. However, the races of the patients were not recorded in the study and the overall mortality among this population was not examined. One of the possible reasons contributing to our result was that warfarin not only increased the risk of bleeding, but may also lead to arterial medial and valvular calcification, as well as calcific uremic arteriopathy (calciaphylaxis) in HD patients [30]. Warfarin reduces the function of Gas-6 and matrix G1a protein (MGP), an inhibitor of vascular calcification [31-33]. In HD patients, the level of inactive MGP is increased and warfarin usage may accelerate vascular calcification [34]. Calciaphylaxis was found in 1-4% of HD patients using warfarin and was associated with high mortality rate and poor outcomes [35-38].

Our study revealed no significant differences in the risks of hemorrhagic stroke and gastrointestinal bleeding between the treatment groups (aspirin, warfarin, and aspirin combined with warfarin) and the non-treatment group. However, previous studies examining the risk of bleeding complications associated with warfarin use in HD patients with AF have yielded inconclusive results [11, 19]. For example, a cohort study from Canada involving 1,626 dialysis patients with AF showed that warfarin users had a 44% higher bleeding risk (95% CI: 1.13-1.85) than nonusers did [11]. Another
study from the Danish cohort examining 901 patients with AF on renal replacement therapy revealed that warfarin and aspirin combined with warfarin groups had no increased bleeding risk (HR: 1.27, \( P = 0.15 \); HR: 1.71, \( P = 0.06 \)) compared with a non-treatment group [19]. However, in the same study, the aspirin group had a significantly higher bleeding risk than that of the non-treatment group (HR: 1.63, \( P = 0.003 \)). The differences in bleeding complications among these studies are unclear, possibly because of differences in race. Our study examined a mainly Chinese population, and previous studies have revealed that warfarin is frequently underused in the Asian population [27, 29].

No prior studies have investigated the cardiovascular outcomes of antithrombotic therapy in HD patients with AF and high thromboembolic risk. Our results revealed no significant differences in cardiovascular outcomes, such as congestive heart disease, acute coronary syndrome, and peripheral arterial occlusive disease, among the treatment and non-treatment groups in HD patients with AF and high thromboembolic risk.

The results of our study were strengthened by using catastrophic illness data provided by the NHIRD, which is one of the world’s most reliable databases and has been widely used in many previous studies [12, 13, 39, 40]. However, some limitations exist in this study. First, the NHIRD does not provide information on variables such as body mass index, smoking or alcohol consumption, dialysis adequacy, and biochemical examination results. Consequently, the HAS-BLED bleeding risk, as recommended by the European Society of Cardiology guideline, could not be calculated because of the lack of data on liver function and the international normalized ratio [31]. Second, we can provide only observational results from the population in the NHIRD.

In conclusion, the mortality rate was not significantly different between the treatment groups (aspirin, warfarin, and aspirin combined with warfarin) and non-treatment group in HD patients with AF and high thromboembolic risk; however, the aspirin combined with warfarin group had a higher mortality rate than that of the aspirin group. In addition, the incidence of ischemic stroke was much higher in the aspirin and the aspirin combined with warfarin groups than that in the non-treatment group. Therefore, usage of aspirin and warfarin in HD patients with AF and high thromboembolic risk should be cautiously evaluated.

Acknowledgements

This study is based on data from the NHIRD, which are provided by the Bureau of NHI and Department of Health and managed by the NHRI. The interpretations and conclusions contained herein do not represent those of the Bureau of NHI, Department of Health, or NHRI. This study was funded by a grant (TCRD 100-56) from Tzu Chi General Hospital, Hualien, Taiwan, and it was presented at the Annual Meeting of the Taiwan Society of Nephrology, Taipei, Taiwan held on 7 and 8 December 2013.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Te-Chao Fang, Division of Nephrology, Department of Internal Medicine, Taipei Medical University Hospital, Taipei Medical University, No. 252, Wuxing Street, Taipei 11031, Taiwan. Tel: +886-2-2737-2181 Ext. 8481; Fax: +886-2-2736-3051; E-mail: fangtechao@ymail.com.tw

References


Antithrombotic therapy on HD patients with AF and high thromboembolic risk


[22] Zimmermann R, Thiessen M, Walter E and Morl H. Paradoxical effect of high and low dose


