Int J Clin Exp Med 2017;10(9):13982-13991
www.ijcem.com /ISSN:1940-5901/IJCEM0053331

Original Article

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

Yu-Hsien Lai[1], Tsung-Cheng Hsieh[2], Chu-Lin Chou[3], Chiu-Huang Kuo[1], Yu-Li Lin[1], Chih-Hsien Wang[1], Te-Chao Fang[4,5]

[1]Division of Nephrology, Department of Internal Medicine, Hualien Buddhist Tzu Chi General Hospital, Hualien, Taiwan; [2]Institute of Medical Sciences, Tzu Chi University, Hualien, Taiwan; [3]Division of Nephrology, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan; [4]Division of Nephrology, Department of Internal Medicine, Taipei Medical University Hospital, Taipei Medical University, Taipei, Taiwan; [5]Division 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 CHA_2DS_2-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 emboli formation in the general population. The CHA_2DS_2-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 CHA_2DS_2-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

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 CHA_2DS_2-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 CHA_2DS_2-VASc score was then calculated for HD patients with a diagnosis of AF. We conducted subgroup analyses of patients with a CHA_2DS_2-VASc score $\geq$ 2, who represented patients with high thromboembolic risk. Four

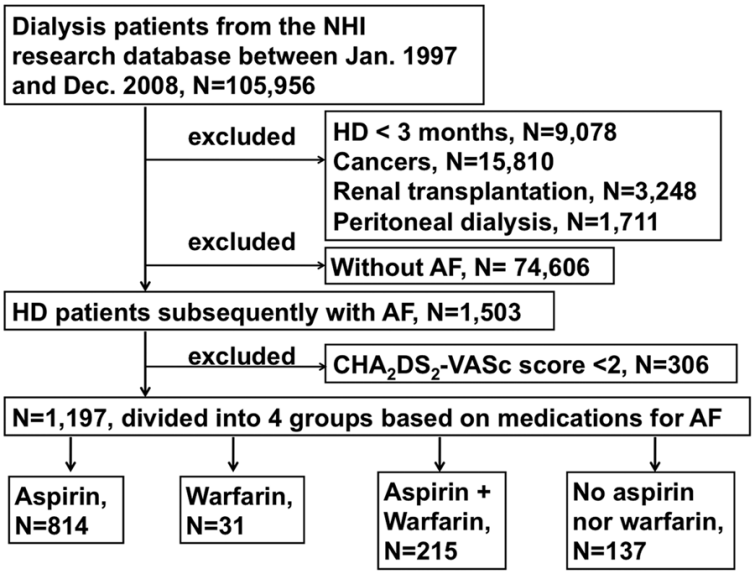

Figure 1. Identification of hemodialysis patients with atrial fibrillation and high thromboembolic risk. N: number of events.

groups of patients, namely aspirin, warfarin, aspirin combined with warfarin, and non-treatment groups, were compared. The index date was defined as the date of AF onset. The follow-up period began from the date of AF onset. The outcomes of the study were total mortality, ischemic stroke (ICD-9: 433, 434, 435, 436), haemorrhagic stroke (ICD-9: 430, 431, 432), congestive heart failure (ICD-9: 398.91, 402.X1, 404.X1, 404.X3, 422, 425, 428), acute coronary syndrome (ICD-9: 410, 411), peripheral arterial occlusive disease (ICD-9: 440, 443, 444, 447, 557), and gastrointestinal bleeding (ICD-9: 531, 532, 533, 537.83, 569.85, 578).

Statistical analysis

The analysed characteristics of the patients in the four groups were sex, age, and previous comorbidities. The differences between these groups were compared using the chi-square test. A Cox proportional hazards model and event-free survival curve were used to assess the impact of independent predictors on the hazard ratios (HRs) of mortality and the adverse outcomes after adjustment for sex, age, and comorbidities in HD patients with high thromboembolic risk. The SAS statistical software (SAS System for Windows version 9.1.3, SAS Institute, Cary, NC, USA) was used for statistical analysis. All statistical tests were 2-sided, and $P < 0.05$ was considered statistically significant.

Results

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 CHA_2DS_2-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

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

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

N, number of cases.

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

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

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

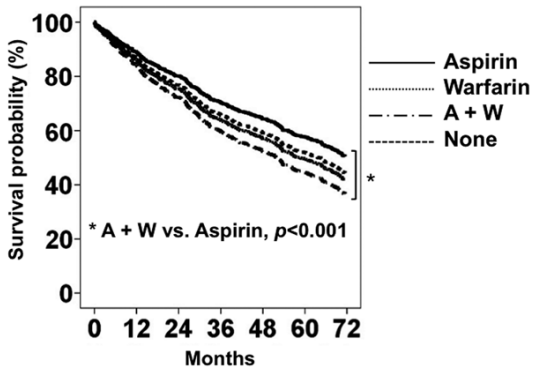

Figure 2. Adjusted survival probability of atrial fibrillation in hemodialysis patients with high thromboembolic risk in the Cox regression model. A+W: aspirin combined with warfarin.

total mortality rate (HR: 0.80, *P* = 0.035; **Table 3**).

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 haemorrhagic stroke (**Figure 3B**), congestive heart failure, gastrointestinal bleeding, peripheral arterial occlusive disease, and acute coronary syndrome (**Figure 4**).

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 haemorrhagic 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

Table 3. Adjusted hazard ratios for total mortality in hemodialysis patients with atrial fibrillation and high thromboembolic risk

	HR	95% CI	*P* value
Treatment vs. Non-treatmentgroups			
Aspirin vs. None	0.84	0.63-1.12	0.234
Warfarin vs. None	1.07	0.60-1.93	0.821
A+W vs. None	1.23	0.88-1.73	0.227
Comparison between treatmentgroups			
Aspirin vs. Warfarin	0.90	0.53-1.51	0.683
A+W vs. Aspirin	1.47	1.16-1.86	< 0.001
A+W vs. Warfarin	1.15	0.65-2.04	0.204
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.

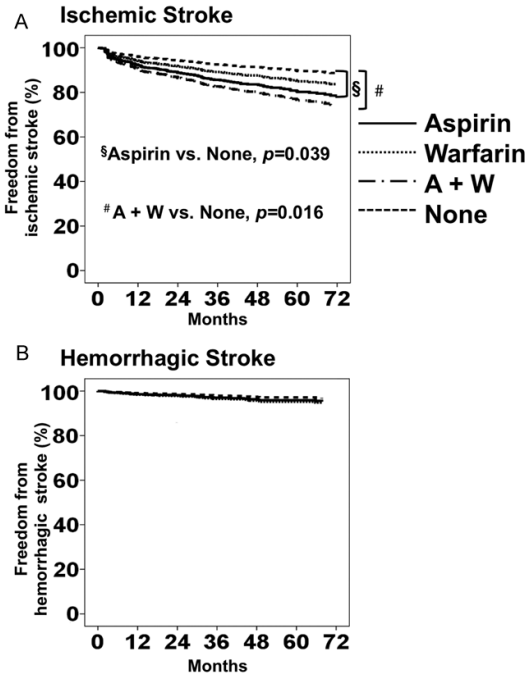

Figure 3. Probability of freedom from stroke in hemodialysis patients with atrial fibrillation and high thromboembolic risk in the Cox regression model. A. Ischemic stroke. B. Haemorrhagic stroke. A+W: aspirin combined with warfarin.

treatment groups and the non-treatment group of HD patients with AF and high thromboembolic risk. Regarding the survival outcome, our 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 hyperlipidemia 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 hyperlipidemia, 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

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

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 I_2 (PGI_2), 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

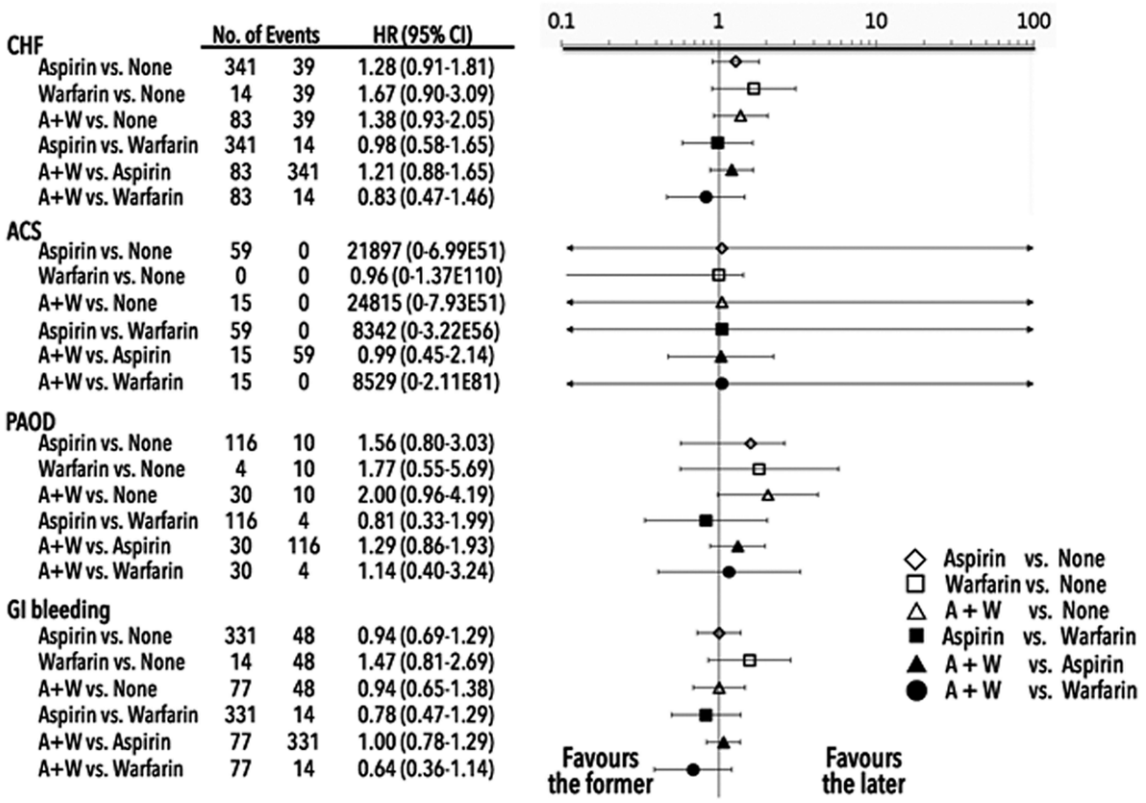

Figure 4. Adjusted hazard ratio (HR) and 95% confidence interval (CI) of outcome events of atrial fibrillation in hemodialysis patients with high thromboembolic risk. A, aspirin; W, warfarin; A+W, aspirin combined with warfarin; GI, gastrointestinal; CHF, congestive heart failure; PAOD, peripheral arterial 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 (calciphylaxis) 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]. Calciphylaxis 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 haemorrhagic 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 ofthe 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@yahoo.com.tw

References

[1] Lip GY, Nieuwlaat R, Pisters R, Lane DA and Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest 2010; 137: 263-272.

[2] Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey JY, Ponikowski P and Rutten FH. Guidelines for the management of atrial fibrillation: the task force for the management of atrial fibrillation of the European society of cardiology (ESC). Eur Heart J 2010; 31: 2369-2429.

[3] Soliman EZ, Prineas RJ, Go AS, Xie D, Lash JP, Rahman M, Ojo A, Teal VL, Jensvold NG, Robinson NL, Dries DL, Bazzano L, Mohler ER, Wright JT, Feldman HI; Chronic Renal Insufficiency Cohort (CRIC) Study Group. Chronic kidney disease and prevalent atrial fibrillation: the chronic renal insufficiency cohort (CRIC). Am Heart J 2010; 159: 1102-1107.

[4] Wizemann V, Tong L, Satayathum S, Disney A, Akiba T, Fissell RB, Kerr PG, Young EW and Robinson BM. Atrial fibrillation in hemodialysis patients: clinical features and associations with anticoagulant therapy. Kidney Int 2010; 77: 1098-1106.
[5] Reinecke H, Brand E, Mesters R, Schabitz WR, Fisher M, Pavenstadt H and Breithardt G. Dilemmas in the management of atrial fibrillation in chronic kidney disease. J Am Soc Nephrol 2009; 20: 705-711.
[6] Apostolakis S, Guo Y, Lane DA, Buller H and Lip GY. Renal function and outcomes in anticoagulated patients with non-valvular atrial fibrillation: the AMADEUS trial. Eur Heart J 2013; 34: 3572-3579.
[7] Falga C, Capdevila JA, Soler S, Rabunal R, Sanchez Munoz-Torrero JF, Gallego P, Monreal M; Investigators R. Clinical outcome of patients with venous thromboembolism and renal insufficiency. Findings from the RIETE registry. Thromb Haemost 2007; 98: 771-776.
[8] Chan KE, Lazarus JM, Thadhani R and Hakim RM. Warfarin use associates with increased risk for stroke in hemodialysis patients with atrial fibrillation. J Am Soc Nephrol 2009; 20: 2223-2233.
[9] Genovesi S and Santoro A. Warfarin and stroke outcomes in hemodialysis patients with atrial fibrillation. J Am Soc Nephrol 2009; 20: 2090-2092.
[10] Hsieh TC, Chou CL, Chen JS, Kuo CH, Wang YC, Lai YH, Lin YL, Wang CH and Fang TC. Risk of mortality and of atherosclerotic events among patients who underwent hemodialysis and subsequently developed retinal vascular occlusion: a Taiwanese retrospective cohort study. JAMA Ophthalmol 2016; 134: 196-203.
[11] Shah M, Avgil Tsadok M, Jackevicius CA, Essebag V, Eisenberg MJ, Rahme E, Humphries KH, Tu JV, Behlouli H, Guo H and Pilote L. Warfarin use and the risk for stroke and bleeding in patients with atrial fibrillation undergoing dialysis. Circulation 2014; 129: 1196-1203.
[12] Lin HF, Li YH, Wang CH, Chou CL, Kuo DJ and Fang TC. Increased risk of cancer in chronic dialysis patients: a population-based cohort study in Taiwan. Nephrol Dial Transplant 2012; 27: 1585-1590.
[13] Kuo CH, Hsieh TC, Wang CH, Chou CL, Lai YH, Chen YY, Lin YL, Wu ST and Fang TC. Increased risks of mortality and atherosclerotic complications in incident hemodialysis patients subsequently with bone fractures: a nationwide case-matched cohort study. PLoS One 2015; 10: e0121705.
[14] Nishimura M, Hashimoto T, Kobayashi H, Fukuda T, Okino K, Yamamoto N, Iwamoto N, Nakamura N, Yoshikawa T and Ono T. The high incidence of left atrial appendage thrombosis in patients on maintenance haemodialysis. Nephrol Dial Transplant 2003; 18: 2339-2347.
[15] Kilpatrick RD, McAllister CJ, Kovesdy CP, Derose SF, Kopple JD and Kalantar-Zadeh K. Association between serum lipids and survival in hemodialysis patients and impact of race. J Am Soc Nephrol 2007; 18: 293-303.
[16] Wanner C, Krane V, Marz W, Olschewski M, Mann JF, Ruf G and Ritz E. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med 2005; 353: 238-248.
[17] Fellstrom BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, Chae DW, Chevaile A, Cobbe SM, Gronhagen-Riska C, De Lima JJ, Lins R, Mayer G, McMahon AW, Parving HH, Remuzzi G, Samuelsson O, Sonkodi S, Sci D, Suleymanlar G, Tsakiris D, Tesar V, Todorov V, Wiecek A, Wuthrich RP, Gottlow M, Johnsson E and Zannad F. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med 2009; 360: 1395-1407.
[18] Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, Wanner C, Krane V, Cass A, Craig J, Neal B, Jiang L, Hooi LS, Levin A, Agodoa L, Gaziano M, Kasiske B, Walker R, Massy ZA, Feldt-Rasmussen B, Krairittichai U, Ophascharoensuk V, Fellstrom B, Holdaas H, Tesar V, Wiecek A, Grobbee D, de Zeeuw D, Gronhagen-Riska C, Dasgupta T, Lewis D, Herrington W, Mafham M, Majoni W, Wallendszus K, Grimm R, Pedersen T, Tobert J, Armitage J, Baxter A, Bray C, Chen Y, Chen Z, Hill M, Knott C, Parish S, Simpson D, Sleight P, Young A and Collins R. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (study of heart and renal protection): a randomised placebo-controlled trial. Lancet 2011; 377: 2181-2192.
[19] Olesen JB, Lip GY, Kamper AL, Hommel K, Kober L, Lane DA, Lindhardsen J, Gislason GH and Torp-Pedersen C. Stroke and bleeding in atrial fibrillation with chronic kidney disease. N Engl J Med 2012; 367: 625-635.
[20] Weber E, Haas TA, Muller TH, Eisert WG, Hirsh J, Richardson M and Buchanan MR. Relationship between vessel wall 13-HODE synthesis and vessel wall thrombogenicity following injury: influence of salicylate and dipyridamole treatment. Thromb Res 1990; 57: 383-392.
[21] Kelton JG, Hirsh J, Carter CJ and Buchanan MR. Thrombogenic effect of high-dose aspirin in rabbits. Relationship to inhibition of vessel wall synthesis of prostaglandin I2-like activity. J Clin Invest 1978; 62: 892-895.
[22] Zimmermann R, Thiessen M, Walter E and Morl H. Paradoxical effect of high and low dose

aspirin in experimental arterial thrombosis. Artery 1980; 8: 422-425.
[23] Buchanan MR and Brister SJ. Individual variation in the effects of ASA on platelet function: implications for the use of ASA clinically. Can J Cardiol 1995; 11: 221-227.
[24] Cambria-Kiely JA and Gandhi PJ. Aspirin resistance and genetic polymorphisms. J Thromb Thrombolysis 2002; 14: 51-58.
[25] Aronoff G, Brater DC, Schrier R and Bennett WM. Use of drugs in patients with renal insufficiency. Workshop report. Blood Purif 1994; 12: 14-19.
[26] Winkelmayer WC, Liu J, Setoguchi S and Choudhry NK. Effectiveness and safety of warfarin initiation in older hemodialysis patients with incident atrial fibrillation. Clin J Am Soc Nephrol 2011; 6: 2662-2668.
[27] Shen AY, Yao JF, Brar SS, Jorgensen MB and Chen W. Racial/ethnic differences in the risk of intracranial hemorrhage among patients with atrial fibrillation. J Am Coll Cardiol 2007; 50: 309-315.
[28] Ma C. Current antithrombotic treatment in East Asia: some perspectives on anticoagulation and antiplatelet therapy. Thromb Haemost 2012; 107: 1014-1018.
[29] Yu HC, Tsai YF, Chen MC and Yeh CH. Underuse of antithrombotic therapy caused high incidence of ischemic stroke in patients with atrial fibrillation. Int J Stroke 2012; 7: 112-117.
[30] Wu CY, Wu MS, Kuo KN, Wang CB, Chen YJ and Lin JT. Long-term peptic ulcer rebleeding risk estimation in patients undergoing haemodialysis: a 10-year nationwide cohort study. Gut 2011; 60: 1038-1042.
[31] Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, Hindricks G, Kirchhof P; Guidelines ESCCfP. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European heart rhythm association. Eur Heart J 2012; 33: 2719-2747.
[32] Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ and Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest 2010; 138: 1093-1100.
[33] Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009; 361: 1139-1151.
[34] Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011; 365: 883-891.
[35] Sood MM, Komenda P, Sood AR, Rigatto C and Bueti J. The intersection of risk and benefit: is warfarin anticoagulation suitable for atrial fibrillation in patients on hemodialysis? Chest 2009; 136: 1128-1133.
[36] Fine A and Zacharias J. Calciphylaxis is usually non-ulcerating: risk factors, outcome and therapy. Kidney Int 2002; 61: 2210-2217.
[37] Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011; 365: 981-992.
[38] Ruff CT, Giugliano RP, Antman EM, Crugnale SE, Bocanegra T, Mercuri M, Hanyok J, Patel I, Shi M, Salazar D, McCabe CH and Braunwald E. Evaluation of the novel factor Xa inhibitor edoxaban compared with warfarin in patients with atrial fibrillation: design and rationale for the Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation-Thrombolysis In Myocardial Infarction study 48 (ENGAGE AF-TIMI 48). Am Heart J 2010; 160: 635-641.
[39] Wang YC, Hsieh TC, Chou CL, Wu JL and Fang TC. Risks of adverse events following coprescription of statins and calcium channel blockers: a nationwide population-based study. Medicine (Baltimore) 2016; 95: e2487.
[40] Chou CL, Hsieh TC, Wang CH, Hung TH, Lai YH, Chen YY, Lin YL, Kuo CH, Wu YJ and Fang TC. Long-term outcomes of dialysis patients after coronary revascularization: a population-based cohort study in Taiwan. Arch Med Res 2014; 45: 188-194.