3）腎血流減少による腎前性腎障害

腎細動脈障害は，腎血流量および糸球体濾過量の低下を引き起こし，腎前性急性腎不全を招く．NSAIDs によるプロスタグランジン（PG）産生阻害を介した腎血流量の低下のほか，レニン・アンジオテンシン系（renin-angiotensin system：RAS）阻害薬は，アンジオテンシンⅡによる AT 1 受容体への作用を減弱させ，輸出細動脈を強く拡張させ，糸球体濾過圧の減少を介して腎機能を低下させる．カルシニューリン阻害薬は輸入細動脈を収縮させ，血流量を低下させる．これにはエンドセリンなどの血管作用性生理活性物質の活性増大や RAS の関与が考えられている．

4）尿細管閉塞性障害（腎後性腎障害）

糸球体濾過や尿細管分泌により尿細管腔内に薬剤が移行した後，尿濃縮による濃度上昇が起こる．その際に生じた析出物が尿細管を閉塞し，腎後性腎障害を引き起こす．

5）糸球体障害（ネフローゼ症候群）

病的な蛋白尿は，1）血中に異常に増加した蛋白が尿細管の再吸収極量を超えて尿中に漏出した場合，2）糸球体上皮細胞・基底膜を中心とする糸球体バリアの機能障害，3）尿細管障害による漏出・再吸収障害，4）尿路系病変からの漏出，などにより生じる．薬剤性蛋白尿は複数の機序が同時に起こることも多い．薬剤による糸球体病変は，糸球体腎炎，微小変化群，膜性腎症，半月体形成性糸球体腎炎（ANCA 関連血管炎），巣状分節性糸球体硬化症などがあり，早期発見による治療介入ができれば蛋白尿，腎機能は改善するとの報告がある．

6）慢性尿細管間質性腎炎

慢性間質性腎炎は亜急性あるいは慢性の経過をとり，腎機能障害により発見される．初期には近位尿細管機能障害による尿細管性アシドーシスや尿糖，アミノ酸尿の出現と，集合尿細管障害による多尿や尿濃縮力，軽度の蛋白尿，血尿がみられる．進行すると糸球体障害，血管障害を伴って，腎機能低下をきたす．原因薬剤は，炭酸リチウム，シスプラチン，シクロスポリン，タクロリムスなどがある．

7）水電解質異常をきたす腎障害[3)]

炭酸リチウムなどは抗利尿ホルモン（antidiuretic hormone：ADH）の作用・分泌障害による尿濃縮障害（腎性尿崩症）をきたし高ナトリウム（Na）血症を呈する．一方，低 Na 血症は，ADH の非生理的な分泌や作用により尿希釈能が障害されて発症し，抗悪性腫瘍薬（シスプラチンなど）や抗うつ薬，NSAIDs などが原因となる．サイアザイド系利尿薬は低 Na 血症をきたすが，尿希釈障害だけでなく，遠位尿細管での Na^+ および Cl^- の再吸収障害と，腎集合管主細胞に達する尿中 Na 量が多いことでカリウム（K）排泄が増加し，低 K 血症が生じる．

8）横紋筋融解症による二次性腎障害[4)]

薬物による筋組織障害により，挫滅症候群（crush syndrome）に類似して，筋細胞の壊死や融解を

生ずることがある．筋細胞から遊出したミオグロビンが腎尿細管を障害し，二次的に急性腎不全を引き起こす．原因薬物として，フィブラート系やスタチン系，抗てんかん薬であるバルプロ酸Naなどが知られている．

文献

1) 武井　卓，新田孝作．腎機能低下をきたす薬剤性腎障害．日腎会誌．2012；54：985-90.
2) 平田純生，門脇大介，成田勇樹．薬剤性腎障害と薬物の適正使用．日腎会誌．2012；54：999-1005.
3) 富永直人，柴垣有吾，木村健二郎．水電解質異常をきたす薬剤性腎障害．日腎会誌．2012；54：911-98.
4) 玄番宗一．薬物による腎機能障害の病態と発症機序．日薬理誌．2006：127；433-40.

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ORIGINAL ARTICLE

Association between warfarin use and incidence of ischemic stroke in Japanese hemodialysis patients with chronic sustained atrial fibrillation: a prospective cohort study

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Abstract
Background Although generally recommended for atrial fibrillation (AF) in the general population, the efficacy and safety of warfarin in hemodialysis patients remains controversial. Warfarin use in hemodialysis patients may confer an additional risk of bleeding that is not appreciated in patients without renal failure because hemodialysis patients have platelet defects and receive anticoagulation agents during dialysis. The incidence of major bleeding was reported to be higher in Japanese AF patients on warfarin therapy compared to patients in other countries, suggesting that racial differences may influence bleeding tendency. Thus, examining risks and benefits of warfarin therapy in Japanese hemodialysis patients with AF is important.
Methods In order to determine associations between warfarin use and new ischemic stroke events, major bleeding, and all-cause mortality, a prospective cohort study of 60 Japanese hemodialysis patients with chronic sustained AF was conducted using Cox proportional modeling and propensity score matching.

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Results The mean patient age was 68.1 years. During 110 person-years of follow-up, 13 ischemic strokes occurred. After adjusting for CHADS2 score, warfarin use was not associated with a significant reduction in ischemic stroke events [hazard ratio (HR) 3.36; 95 % confidence interval (CI) 0.94–11.23]. Similar results were obtained after propensity score matching (HR 3.36; 95 % CI 0.67–16.66). Warfarin use was not associated with significant increases in major bleeding or all-cause mortality.
Conclusions These results suggest that warfarin may not prevent ischemic stroke in Japanese hemodialysis patients with chronic sustained AF. Adequately powered studies are needed to determine the risks and benefits of anticoagulation therapy in these patients.

Keywords Brain infarction · Cohort studies · Hemorrhage · Mortality · Propensity score

Introduction

Dialysis patients have a 3.5-fold higher mortality rate due to ischemic and hemorrhagic stroke than the general population in Japan [1]. They also have an increased risk of atrial fibrillation (AF) [2]. In the general population, AF is associated with an increased risk of stroke frequently estimated using the CHADS2 score, which is derived by assigning one point for history of congestive heart failure, age >75 years, or diabetes mellitus, and two points for prior stroke or transient ischemic attack (TIA) [3]. Anticoagulation therapy with warfarin is recommended for patients with a CHADS2 score ≥2 [4, 5]. Although warfarin likely increases the risk of intracranial bleeding, the absolute risk is low [6]. Thus, warfarin is highly effective for prophylaxis of ischemic stroke in the general population [6].

However, the risk–benefit ratio of warfarin therapy is unclear in hemodialysis patients. Due to the prevalence of congestive heart failure, hypertension, and diabetes mellitus, the majority of hemodialysis patients with AF would require warfarin anticoagulation based on their CHADS2 score. Results from recent observational studies on the effects of warfarin on ischemic stroke are controversial [7–11]. No randomized trials have evaluated the efficacy of warfarin for prophylaxis of ischemic stroke in hemodialysis patients. Warfarin use in hemodialysis patients may confer an additional risk of bleeding that is not appreciated in patients without end-stage kidney disease because hemodialysis patients have several platelet defects and receive anticoagulation treatments during dialysis. In addition, the incidence of major bleeding and intracranial hemorrhage was reported to be higher in Japanese non-rheumatic AF patients on low-dose warfarin therapy compared to patients in Western countries, suggesting that racial differences exist regarding bleeding tendency with warfarin treatment [12]. Thus, it is necessary to examine the risks and benefits of warfarin therapy in Japanese hemodialysis patients with AF.

This study aimed to examine associations between warfarin use and new ischemic stroke, major bleeding, and all-cause mortality in Japanese hemodialysis patients with AF.

Methods

Study population and design

A prospective multicenter cohort study was conducted between March 2008 and February 2011. Inclusion criteria were patients aged ≥20 years with end-stage kidney disease requiring hemodialysis and preexisting chronic sustained AF. Patients with paroxysmal AF were excluded. Patients with a prosthetic heart valve were also excluded due to mandatory recommended warfarin therapy. Patients were dialyzed three times per week at 14 facilities (35 % hospital-based and 65 % clinic). All patients provided written informed consent prior to participation. The ethics committee at Niigata University Hospital approved the study protocol (No. 616).

Outcome, exposure, and baseline covariates

The primary endpoint for the study was new ischemic stroke (fatal or nonfatal). New ischemic stroke was defined as a rapid onset focal neurologic deficit persisting for >24 h confirmed by imaging techniques, such as computed tomography or nuclear magnetic resonance demonstrating the absence of hemorrhagic causes. TIA was not included as a primary endpoint because it is often clinical and may be prone to subjective clinical interpretation. Secondary endpoints included major bleeding and death from any cause. Major bleeding was defined as fatal bleeding or bleeding that required hospitalization [13]. Information regarding cause of death was obtained by the patients' nephrologist. Cause of death was classified based on Japanese Society for Dialysis Therapy definitions [14].

Demographic characteristics, cause of end-stage kidney disease, cardiovascular risk factors, medication use, laboratory data, and dialysis data (duration of hemodialysis session, type of vascular access, and single-pooled *Kt/V*) were collected. Baseline stroke risk was assessed using CHADS2 scores, as described in the recent Japanese guideline [5]. A high CHADS2 score corresponds to a greater risk of stroke both in the general population [3] and in hemodialysis patients [2]. Because hemodialysis patients retain fluid

between sessions, we assumed that all hemodialysis patients had congestive heart failure. Hypertension was defined as use of antihypertensive medication, predialysis systolic blood pressure ≥140 mmHg, and/or predialysis diastolic blood pressure ≥90 mmHg. Diabetes was defined based on patient medical history reported by the nephrologist. Body mass index was calculated as weight in kilograms divided by height in meters squared. Information about recent medications used, including antiplatelet drugs, histamine-2-blocker or proton pump inhibitors, erythropoiesis-stimulating agents (ESAs), and anti-hypertensive agents, was also collected. As frailty indicators, modes of transport to dialysis facilities were categorized as walking alone without a cane, walking alone with a cane, walking with a support person, in a wheelchair, or on a stretcher. Blood samples were collected prior to each dialysis session. Single-pooled *Kt/V* was calculated using the Daugirdas equation [15].

Statistical analysis

Data for continuous variables are presented as the mean and standard deviation (SD) or the median and 25th and 75th percentiles. Categorical variables are presented as frequencies with percentages. Differences in variables between patients using and not using warfarin were evaluated by chi-squared or Fisher's exact test for categorical variables and Student's *t* test or Mann–Whitney *U* test for continuous variables.

Time-to-event methods (Kaplan–Meier survival curves and Cox proportional-hazards models) were used to compare patients using and not using warfarin with respect to event rates of new ischemic stroke, major bleeding, or all-cause mortality. Repeat events were not considered.

Subsidiary analyses were conducted to assess the robustness of key results. First, the primary analysis was intention-to-treat in which patients who started using warfarin after study enrollment were not reclassified. To account for possible longitudinal changes in drug prescription over time, an additional validation analysis was performed in which the primary analysis was repeated and patients were censored when warfarin use changed. Second, due to the limited size of the cohort [16], supplementary Kaplan–Meier analysis with the log-rank test and Cox regression analyses were performed using a propensity score (PS), which considers each individual's probability of exposure to confounding variables, including age, gender, dialysis vintage, height, cause of end-stage kidney disease, dialysis facilities, type of vascular access, history of hemorrhagic stroke, ESA use, CHADS2 score, single-pooled *Kt/V*, mode of transport to dialysis facilities, and use of antiplatelet agents [17].

$P < 0.05$ was considered statistically significant using two-tailed tests. All statistical analyses were performed with the SPSS statistical package for Windows (Version 18.0 SPSS, Chicago, USA).

Results

A total of 60 hemodialysis patients with chronic sustained AF were enrolled in this study. All of the enrolled patients were analyzed. The cohort included 39 male and 21 female hemodialysis patients with a mean age of 68.1 years (SD 8.9), a mean body mass index of 20.6 kg/m^2 (SD 2.9), and median duration on dialysis of 10 years (range 0–38). All patients were dialyzed three times a week for 3–5 h. Glomerulonephritis was the most common cause of end-stage kidney disease (55 %), followed by diabetes (23 %). Antiplatelet medications included aspirin, ticlopidine, and cilostazol.

At enrollment, 28 (47 %) patients were already receiving warfarin and 32 (53 %) were not. Warfarin users tended to be younger with a longer dialysis vintage than non-users, but did not show differences in CHADS2 scores and use of antiplatelet agents (Table 1). Warfarin users also had higher high-density lipoprotein cholesterol levels and a higher prevalence of ESA use. Female gender and diabetes were less common among warfarin users than non-users. The mean baseline international normalized ratio (INR) in warfarin users was 1.5 (SD 0.4).

The cohort was followed for a total of 110 person-years. The rate of ischemic stroke was 11.8 per 100 person-years, which increased with higher CHADS2 scores (Table 2). Warfarin users were more likely to have new ischemic stroke compared with non-users [hazard ratio (HR) 1.94] (Table 3; Fig. 1a). However, there were too few cases to provide individual HR estimates [95 % confidence interval (CI) 0.63–5.93]. After adjusting for CHADS2 score as a continuous variable the HR increased (HR 3.36; 95 % CI 0.94–11.23) (Table 4). The CHADS2 score covariate significantly influenced the risk of ischemic stroke in the Cox model (HR 2.02; 95 % CI 1.27–3.23).

Because warfarin use changed in several patients during the study, the primary analysis was repeated by censoring these patients. The risk did not change as a result of censoring (Table 4; Fig. 1b). To adjust for differences in baseline characteristics between warfarin users and non-users, we repeated the primary analysis in a PS-matched cohort, and all observed variables were successfully balanced (Table 5). A similar association was observed in the PS-matched cohort (Table 4; Fig. 1c).

Risk of major bleeding, which occurred at a rate of 5.99 events per 100 person-years, did not differ based on warfarin use (HR 0.85; 95 % CI 0.19–3.64) (Fig. 2a). There were 1.65 hemorrhagic strokes per 100 person-years of follow-up and all-cause mortality exceeded 14.2 deaths per

Table 1 Baseline characteristics of 60 hemodialysis patients with atrial fibrillation and warfarin use

Baseline characteristics	Users ($n = 28$)	Non-users ($n = 32$)	P value
Age (years)	67.8 (9.4)	68.4 (8.5)	0.80
Male [n (%)]	16 (57)	23 (72)	0.28
Body mass index (kg/m^2)	20.7 (3.1)	20.6 (2.8)	0.90
Duration of dialysis (years)	15 (4, 30)	10 (3, 22)	0.33
Cause of end-stage kidney disease			0.61
Glomerulonephritis [n (%)]	16 (57)	17 (53)	
Diabetes [n (%)]	5 (18)	9 (28)	
Other [n (%)]	7 (25)	6 (19)	
Type of vascular access			1.00
Fistula [n (%)]	21 (75)	23 (72)	
Graft [n (%)]	6 (21)	8 (25)	
Superficial artery [n (%)]	0 (0)	1 (3)	
Unknown [n (%)]	1 (4)	0 (0)	
Medical history			
Ischemic stroke [n (%)]	4 (14)	8 (26)	0.34
Transient ischemic attack [n (%)]	0 (0)	3 (10)	0.24
Hemorrhagic stroke [n (%)]	1 (4)	0 (0)	0.47
Coronary artery bypass graft [n (%)]	2 (7)	1 (3)	0.59
Percutaneous coronary intervention [n (%)]	2 (7)	2 (6)	1.00
Malignancy [n (%)]	5 (18)	4 (13)	0.73
Medication			
Antiplatelet drug [n (%)]	17 (61)	15 (47)	0.31
Histamine-2 blocker or PPI [n (%)]	16 (60)	14 (44)	0.30
ESA [n (%)]	23 (81)	21 (66)	0.06
Anti-hypertensive drug [n (%)]	13 (46)	16 (50)	1.00
Comorbidities			
Diabetes mellitus [n (%)]	6 (21)	9 (28)	0.77
Predialysis systolic blood pressure (mmHg)	144 (26)	149 (23)	0.43
Predialysis diastolic blood pressure (mmHg)	76 (15)	83 (19)	0.14
Laboratory parameters			
Serum albumin (mg/dL)	3.8 (0.4)	3.8 (0.3)	0.58
Hemoglobin (g/dL)	10.4 (1.3)	10.7 (1.3)	0.47
Total cholesterol (mg/dL)	155 (34)	154 (29)	0.92
HDL cholesterol (mg/dL)	52 (15)	43 (13)	0.02
Triglyceride (mg/dL)	87 (64, 123)	80 (62, 116)	0.90
HbA1c (%)[a]	5.2 (0.8)	7.3 (2.7)	0.09
PT INR	1.5 (0.4)	NA	NA
Single-pooled *Kt/V*	1.43 (0.60)	1.44 (0.37)	0.96
Ultrafiltration/h (mL/h)	660 (157)	637 (276)	0.69
Transport to dialysis facilities			1.00
Walk alone without a cane [n (%)]	19 (68)	22 (69)	
Walk alone with a cane [n (%)]	3 (11)	3 (9)	
Walk with support person [n (%)]	1 (4)	2 (6)	
Wheelchair [n (%)]	5 (18)	5 (16)	
Stretcher [n (%)]	0 (0)	0 (0)	
CHADS2 score[b]			0.72
1 [n (%)]	5 (19)	3 (10)	
2 [n (%)]	12 (44)	12 (39)	
3 [n (%)]	6 (22)	7 (23)	
4 [n (%)]	2 (13)	4 (13)	
5 [n (%)]	2 (7)	5 (16)	
6 [n (%)]	0 (0)	0 (0)	

Mean (standard deviation), median (interquartile range)

PPI proton pump inhibitor, *ESA* erythropoiesis-stimulating agents, *HDL* high-density lipoprotein, *PT INR* prothrombin time international normalized ratio, *NA* not available

[a] Only diabetic patients

[b] One patient in each group was not included in the calculations due to missing data

Table 2 Incidence rates of ischemic stroke in hemodialysis patients with atrial fibrillation by CHADS2 score

CHADS2 score	Patients (n)	Stroke events (n)	Incidence rate[a] (95 % CI)
0	0	0	NA
1	8	0	0
2	24	3	5.3 (1.1–15.6)
3	13	5	26.1 (8.5–60.9)
4	6	1	10.3 (0.3–57.6)
5	7	3	72.0 (14.8–210.4)
6	0	0	NA
Unknown[b]	2	1	22.2 (0.6–123.8)
Overall	60	13	11.8 (6.3–20.2)

CI confidence interval, *NA* not available

[a] Per 100 person-years

[b] Two patients were not included in the calculations due to missing data

100 person-years (HR 1.00; 95 % CI 0.40–2.52) (Fig. 2b), neither of which differed between warfarin users and non-users. Regarding cause of death, cardiac failure was less common among warfarin users than non-users (Table 6).

Discussion

In this prospective cohort study of Japanese hemodialysis patients with chronic sustained AF, warfarin use was not associated with a significant reduction in ischemic stroke events after adjusting for CHADS2 score or after PS matching. Although limited by the small sample size, these findings suggest that warfarin, which is generally used to prevent future stroke in patients with AF, may not prevent ischemic stroke in Japanese hemodialysis patients. This study highlights the urgent need for adequately powered studies to determine the risks and benefits of anticoagulation therapy in these patients.

Although the observed association between ischemic stroke and warfarin use in this study may disagree with general recommendations for stroke prevention, there is a growing body of similar evidence indicating that warfarin may instead be harmful in hemodialysis patients with AF. Warfarin use in hemodialysis patients with pre-existing AF has been reported to be associated with a two-fold greater risk of new ischemic stroke [8]. A retrospective study reported a three-fold higher risk of stroke, including both ischemic and hemorrhagic, in patients treated with salicylates or warfarin [7]. Another study showed that warfarin use was significantly associated with hemorrhagic (HR 2.38; 95 % CI 1.15–4.96) rather than ischemic (HR 0.92; 95 % CI 0.61–1.37) stroke among older hemodialysis patients with incident AF [10]. Taken together, warfarin may increase risk of stroke (ischemic or hemorrhagic) in hemodialysis patients with AF.

In contrast, some reports have demonstrated associations between warfarin use and a decreased risk of stroke [9, 11]. Warfarin use was associated with a significantly decreased risk of stroke or systemic thromboembolism among patients requiring renal-replacement therapy (HR 0.44; 95 % CI 0.26–0.74) [11]. However, this study included not

Table 3 Number of events, incidence rates, and unadjusted hazard ratios for all study outcomes and warfarin use

Outcome	Warfarin	Number of events	Incidence rate[a] (95 % CI)	Unadjusted hazard ratio (95 % CI)
Ischemic stroke	Users	8	14.8 (6.4–29.2)	1.94 (0.63–5.93)
	Non-users	5	8.9 (2.9–20.8)	
Major bleeding	Users	3	5.3 (1.1–15.5)	0.85 (0.19–3.64)
	Non-users	4	6.6 (1.8–17.0)	
All-cause mortality	Users	9	14.2 (6.5–26.9)	1.00 (0.40–2.52)
	Non-users	9	14.2 (6.5–26.9)	

CI confidence interval

[a] Per 100 person-years

Table 4 Predicted hazard ratios for new ischemic stroke and warfarin use

Models	Hazard ratio (95 % CI)
Intention-to-treat	
Unadjusted	1.94 (0.63–5.93)
Adjusted for CHADS2 score	3.36 (0.94–11.23)
Matched by propensity score	3.36 (0.67–16.66)
Patients censored due to changes in warfarin use	
Unadjusted	1.84 (0.62–5.63)
Adjusted for CHADS2 score	3.17 (0.92–10.93)
Matched by propensity score	3.21 (0.65–15.95)

CI confidence interval

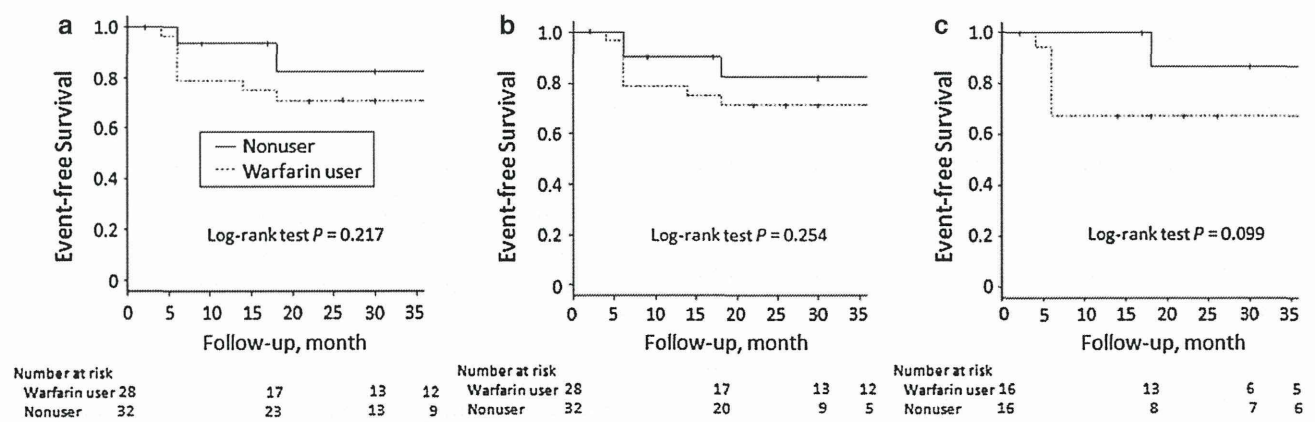

Fig. 1 Crude ischemic stroke survival curves and warfarin use. **a** Under an intention-to-treat assumption, warfarin users were more likely to have new ischemic stroke than non-users. **b** Similar results were noted in censored patients who changed warfarin use after enrollment. **c** Similar results were observed in the propensity score-matched cohort

Table 5 Propensity-score matching and characteristics of the study cohort

Baseline characteristics	Users ($n = 16$)	Non-users ($n = 16$)	P value
Age (years)	70.9 (9.8)	68.1 (9.1)	0.41
Male gender [n (%)]	8 (50)	6 (38)	0.72
Body mass index (kg/m^2)	20.9 (3.7)	20.8 (2.2)	0.91
Duration of dialysis (years)	12 (3, 30)	11 (2, 24)	0.79
Cause of end-stage kidney disease			1.00
Glomerulonephritis [n (%)]	9	10	
Diabetes [n (%)]	3	3	
Other [n (%)]	4	3	
Type of vascular access			1.00
Fistula [n (%)]	13	12	
Graft [n (%)]	3	4	
Medical history			
Ischemic stroke [n (%)]	4	4	1.00
Transient ischemic attack [n (%)]	0	2	0.48
Hemorrhagic stroke [n (%)]	0	0	
Coronary artery bypass graft [n (%)]	2	1	1.00
Percutaneous coronary intervention [n (%)]	2	1	1.00
Malignancy [n (%)]	1	4	0.17
Medication			
Antiplatelet drug [n (%)]	10	10	1.00
Histamine-2 blocker or PPI [n (%)]	9	6	0.48
ESA [n (%)]	13	11	0.69
Anti-hypertensive drug [n (%)]	7	8	1.00
Comorbidities			
Diabetes mellitus [n (%)]	3	3	1.00
Predialysis systolic blood pressure (mmHg)	139 (26)	147 (21)	0.40
Predialysis diastolic blood pressure (mmHg)	79 (16)	82 (20)	0.64
Laboratory data			
Serum albumin (mg/dL)	3.7 (0.3)	3.9 (0.2)	0.20
Hemoglobin (g/dL)	10.5 (1.4)	10.8 (1.4)	0.59
Total cholesterol (mg/dL)	148 (23)	165 (31)	0.09
HDL cholesterol (mg/dL)	49 (15)	45 (14)	0.56
Triglyceride (mg/dL)	78 (61, 123)	86 (63, 154)	0.38
HbA1c (%)[a]	5.6 (0.6)	6.9 (0.6)	0.06
Single-pooled Kt/V	1.50 (0.20)	1.49 (0.46)	0.92
Ultrafiltration/h (mL/h)	687 (183)	761 (243)	0.34
Transport to dialysis facilities			1.00
Walk alone without a cane [n (%)]	11	12	
Walk alone with a cane [n (%)]	1	2	
Walk with support person [n (%)]	1	0	
Wheelchair [n (%)]	3	2	
Stretcher [n (%)]	0	0	
CHADS2 score			1.00
1	2	2	
2	6	7	
3	4	3	
4	2	1	
5	2	3	
6	0	0	

Mean (standard deviation), median (interquartile range)

PPI proton pump inhibitor, *ESA* erythropoiesis-stimulating agents, *HDL* high-density lipoprotein

[a] Only diabetic patients

only hemodialysis patients but also peritoneal dialysis or kidney transplant patients. Because these patients had widely varying exposures to heparin, risks for stroke might differ among these patients. In addition, aspirin use was associated with a significantly increased risk of stroke or systemic thromboembolism among patients without kidney disease [11]. The authors suggest that confounding by indication may be present in this study, given that the result was inconsistent with previous metaanalysis of randomized trials [6]. Another study showed that hemodialysis patients with AF treated with warfarin to maintain an INR between 2.0 and 3.0 had a significant reduction in thromboembolic stroke and an insignificant increase in major bleeding [9]. In the present study, the warfarin dose may not have been sufficient to decrease the risk of ischemic stroke because the patients had a mean INR of 1.5 (SD 0.4). However, another study has shown positive relationships between INR and stroke, and patients with an INR between 2.0 and 3.0 had a significantly higher risk of stroke [8]. Because there are no randomized trials to test the efficacy of warfarin for prophylaxis of ischemic stroke in hemodialysis patients with AF, associations between warfarin use and adverse effects in observational studies may be due to confounding by indication. Warfarin use to reduce the risk of stroke in hemodialysis patients with AF remains controversial.

It is plausible that pre-existing platelet dysfunction and routine use of heparin during hemodialysis may reduce the risk of ischemic stroke in patients with end-stage kidney disease and AF, thereby reducing potential benefits and increasing the potential risk of warfarin anticoagulation [4].

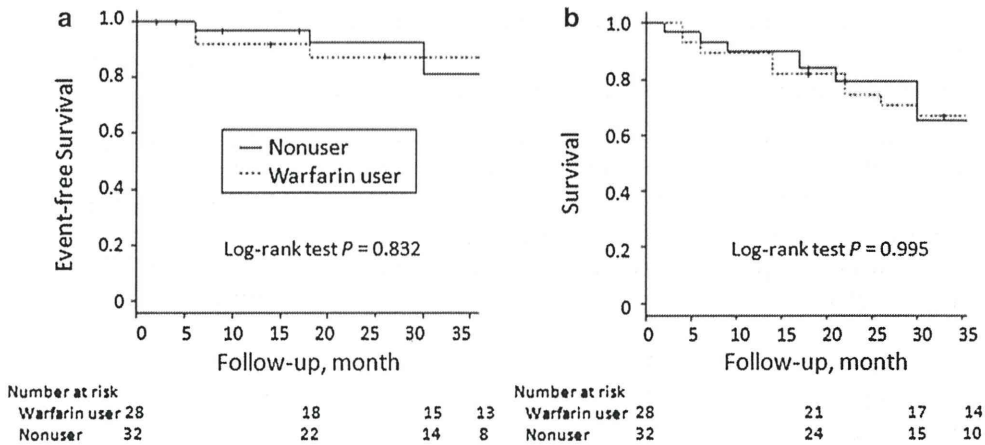

Fig. 2 Crude major bleeding and all-cause mortality survival curves and warfarin use. Warfarin use was not associated with significant increases in major bleeding (**a**) or all-cause mortality (**b**)

Table 6 Cause of death and warfarin use at baseline

Cause of death	Warfarin user ($n = 9$)	Non-users ($n = 9$)
Cardiac failure	2	4
Infectious disease	2	2
Hemorrhage	2	1
Malignant tumor	0	1
Cachexia/uremia	1	0
Suicide	1	0
Unknown	1	1

In addition, warfarin may potentiate vascular calcification and increase the risk of ischemic stroke [18]. Additional detailed studies are required to determine the risks and benefits of warfarin use in hemodialysis patients.

There are several limitations to this study. First, subject selection bias may exist. The rate of ischemic stroke and percentage of warfarin users were higher than in previous reports [2, 8, 10]. This potential selection bias may limit generalizability. Second, patients were on warfarin therapy at the time of enrollment, which implies that they tolerated the therapy well. This may have biased the sample because patients who were unable to tolerate warfarin had already been eliminated. The incidence of bleeding events may have been higher if patients who had just started taking warfarin therapy at enrollment were included. Third, the outcome of stroke was not adjudicated under the research protocol, and diagnosis of stroke may have been preferentially favored in high-risk patients who were more likely to be on warfarin. In addition, due to the limited outcome size, we could only use a limited number of covariates for adjustment [17]. The increase in stroke among warfarin users may have been due to an inherently higher baseline stroke risk that was not fully adjusted for by covariates. Fourth, there could be residual confounding after PS matching. Although PS is powerful for reducing bias in observational studies, it is difficult to remove all bias, and it is not possible for a matching method to balance unmeasured confounders. Finally, the lack of a difference in incidence of ischemic stroke between warfarin users and nonusers may have been due to the limited power of the study (67.1 % for a two-sided 0.05 significance test).

Despite these limitations, the data provide a basis and indicate the need for future research. In particular, the results of our study would be useful for calculating adequate sample size, which is an important component of clinical research. We could not adequately calculate sample size when we initiated this study in 2008, given that such issues had not been raised in the field. Our present results may help estimate an adequate sample size for conducting a large-scale, long-term longitudinal study in Japanese hemodialysis patients with AF. Moreover, to the best of our knowledge, this is the first study that provides information about the risks and benefits of warfarin use in Japanese hemodialysis patients with AF. Because racial differences may influence bleeding tendency with warfarin use [12], this study provides important information for clinicians who treat hemodialysis patients in Japan.

In conclusion, our results suggest that warfarin use may not prevent ischemic stroke in hemodialysis patients with chronic sustained AF. Adequately powered studies are urgently needed to determine the risks and benefits of warfarin therapy in these patients.

Conflict of interest The authors have declared that no conflict of interest exists.

References

1. Wakasugi M, Kazama JJ, Yamamoto, Kawamura K, Narita I. Cause-specific excess mortality among dialysis patients: comparison with the general population in Japan. Ther Apher Dial. Article first published online: 11 Dec 2012. doi:10.1111/j.1744-9987.2012.01144.x.

2. Wizemann V, Tong L, Satayathum S, Disney A, Akiba T, Fissell RB, et al. Atrial fibrillation in hemodialysis patients: clinical features and associations with anticoagulant therapy. Kidney Int. 2010;77:1098–106.
3. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA. 2001;285:2864–70.
4. Zimmerman D, Sood MM, Rigatto C, Holden RM, Hiremath S, Clase CM. Systematic review and meta-analysis of incidence, prevalence and outcomes of atrial fibrillation in patients on dialysis. Nephrol Dial Transplant. 2012;27:3816–22.
5. Ogawa S, Aizawa Y, Atarashi H, Inoue H, Okumura K, Kamakura S, et al. Guidelines for pharmacotherapy of atrial fibrillation. Circ J. 2008;72(Suppl. IV):1639–58 (in Japanese).
6. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med. 2007;146:857–67.
7. Wiesholzer M, Harm F, Tomasec G, Barbieri G, Putz D, Balcke P. Incidence of stroke among chronic hemodialysis patients with nonrheumatic atrial fibrillation. Am J Nephrol. 2001;21:35–9.
8. Chan KE, Lazarus JM, Thadhani R, Hakim RM. Warfarin use associates with increased risk for stroke in hemodialysis patients with atrial fibrillation. J Am Soc Nephrol. 2009;20:2223–33.
9. Lai HM, Aronow WS, Kalen P, Adapa S, Patel K, Goel A, et al. Incidence of thromboembolic stroke and of major bleeding in patients with atrial fibrillation and chronic kidney disease treated with and without warfarin. Int J Nephrol Renovasc Dis. 2009;2:33–7.
10. Winkelmayer WC, Liu J, Setoguchi S, Choudhry NK. Effectiveness and safety of warfarin initiation in older hemodialysis patients with incident atrial fibrillation. Clin J Am Soc Nephrol. 2011;6:2662–8.
11. Olesen JB, Lip GY, Kamper AL, Hommel K, Køber L, Lane DA, et al. Stroke and bleeding in atrial fibrillation with chronic kidney disease. N Engl J Med. 2012;367:625–35.
12. Suzuki S, Yamashita T, Kato T, Fujino T, Sagara K, Sawada H, et al. Incidence of major bleeding complication of warfarin therapy in Japanese patients with atrial fibrillation. Circ J. 2007;71:761–5.
13. Johnson JA. Warfarin: an old drug but still interesting. Pharmacotherapy. 2008;28:1081–3.
14. Nakai S, Iseki K, Itami N, Ogata S, Kazama JJ, Kimata N, et al. An overview of regular dialysis treatment in Japan (as of 31 December 2010). Ther Apher Dial. 2012;16:483–521.
15. Daugirdas JT. Second generation logarithmic estimates of single-pool variable volume Kt/V: an analysis of error. J Am Soc Nephrol. 1993;4:1205–13.
16. Cepeda MS, Boston R, Farrar JT, Strom BL. Comparison of logistic regression versus propensity score when the number of events is low and there are multiple confounders. Am J Epidemiol. 2003;158:280–7.
17. D'Agostino RB Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Stat Med. 1998;17:2265–81.
18. Clase CM, Holden RM, Sood MM, Rigatto C, Moist LM, Thomson BK, et al. Should patients with advanced chronic kidney disease and atrial fibrillation receive chronic anticoagulation? Nephrol Dial Transplant. 2012;27:3719–24.