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Original Paper

Risk of Cerebral Infarction in Japanese Hemodialysis Patients: Miyazaki Dialysis Cohort Study (MID study)

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Key Words
End stage renal disease • Hemodialysis • Cerebral infarction • Risk factor

Abstract
Background/Aims: Predictors including the preventive effects of antiplatelet and anticoagulant drugs on cerebral infarction (CI) events have not yet been clarified in dialysis patients. The aim of the present study was to examine the risk of CI and preventive effects of these drugs in Japanese hemodialysis patients. ***Methods:*** Patients receiving maintenance hemodialysis (n=1,551, median age (interquartile range), 69.0 (59.0-78.0) years; 41.5% female) were enrolled in the Miyazaki Dialysis Cohort Study and prospectively followed-up for 3 years. Kaplan-Meier and Cox's regression analyses were used to clarify the risk of CI. ***Results:*** Eighty-four patients developed CI at an incidence of 21.5/1000 patients per year. The presence of a previous history of CI, atrial fibrillation (AF), and diabetes mellitus in addition to age were also identified as predictive factors for new CI, whereas no relationship was observed between antiplatelet and/or anticoagulant usage and CI. Furthermore, no significant difference was noted in the frequency of CI events between patients with AF who received warfarin and those who did not. ***Conclusions:*** The incidence of CI was higher in dialysis patients with a previous history of CI and AF; however, the preventive effects of antiplatelet/anticoagulant drugs on the development of CI were not evident.

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Introduction

The incidence and prevalence of cerebrovascular diseases is high in patients receiving dialysis. The confirmed incidence of cerebral infarction (CI) was previously reported to be 2.2~50.1/1000 patients per year, which is five- to several ten-fold higher than that in the general population [1-5]. Some risk factors for stroke, such as sex, age, hypertension, and diabetes mellitus, are common between dialysis patients and the general population. Although the reason why strokes occur more frequently in dialysis patients than in the general population is not fully understood, advanced atherosclerosis and the high incidence and prevalence of atrial fibrillation (AF) [6-8] in dialysis patients may be related to the higher incidence of cerebrovascular diseases.

AF was previously reported to be associated with an increased risk of stroke and death in dialysis patients as well as in the general population [6]. In the general population, anticoagulation with warfarin was shown to be effective for both the primary and secondary prevention of cardiogenic cerebral embolisms associated with AF [9]. Antiplatelet therapy was also found to be protective in most types of patients at high risk of occlusive vascular events [10, 11], and combination therapy with antiplatelet and anticoagulation agents is sometimes performed to more effectively prevent vascular events [12]. However, the benefits of warfarin therapy on the onset of cerebral embolism in hemodialysis patients remain controversial; several studies showed that warfarin therapy increased the risk of bleeding, but did not reduce the risk of stroke [13-17]. Furthermore, it has not yet been established whether combination therapy with antiplatelet and anticoagulation agents decreases the risk of CI events in dialysis patients.

Therefore, we prospectively examined the relationship between the onset of CI and these drugs in Japanese hemodialysis patients.

Subjects and Methods

The Miyazaki Dialysis Cohort study (MID study) is a prospective observational study of maintenance HD patients from 27 dialysis centers and was initiated by the University of Miyazaki, Japan. A total of 1,551 patients were enrolled in this cohort study in December, 2009 and were followed-up for 3 years. Exclusion criteria were 1) patients with acute renal failure, 2) hospitalized patients, 3) patients under 18 years of age, and 4) patients who did not agree to this study. Information on physical characteristics, laboratory data, basal renal diseases, comorbidities, and medications was collected by doctors in each dialysis center at the start of the study. Cerebrovascular events (acute myocardial infarction, *de novo* angina pectoris, revascularization, congestive heart failure, stroke, and limb amputation), infections, the new onset of malignancies, and all causes of death were checked monthly by nursing staff or medical doctors during the follow-up periods using questionnaires. Check sheets were collected annually.

The diagnosis of CI was determined using head CT/MRI in addition to typical symptoms and medical examination findings. AF was diagnosed using electrocardiograms conducted at the enrollment. Pre-HD blood pressure was measured in the supine position. Blood pressure values were averaged from 3 consecutive HD sessions during the week of patient enrollment. Survival time was defined as the time from enrollment to individual outcomes, the data for which were collected longitudinally during the course of the study follow-up until December 2012.

Statistical analysis

Descriptive analyses were calculated to describe variables such as the patient characteristics of groups distributed according to developed CI or not. All continuous variables were tested for normal distribution, and Student t-test (for normal distribution) or Mann-Whitney test (for non-normal distribution) was applied for the comparison of the two groups. Crude survival in the exposure group was determined using a Kaplan-Meier analysis with the log-rank test. Cox's regression analysis using backward variable selection with a variable exit criteria set was used to progressively adjust for baseline covariates. All covariates were checked

whether detected to depart significantly from the proportionality assumption by the Kaplan-Meier method and the log-minus-log survival plots. All statistical analyses were performed with SPSS Statistics 20 (IBM Company, Chicago, USA).

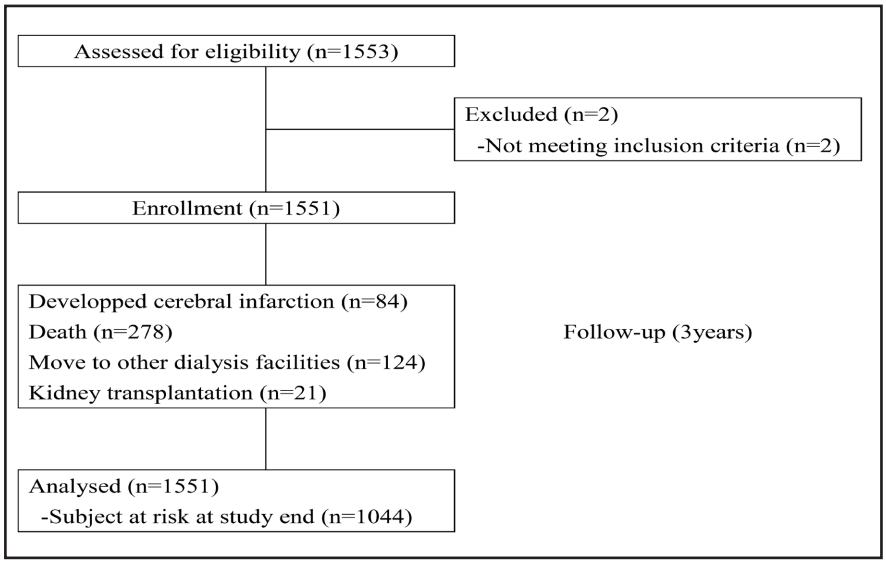

Fig. 1. Flow of patients through the study.

Ethical Considerations

Although this was an observational study, Institutional Review Boards in the University of Miyazaki approved the present study. Data collection was performed in a manner that maintained patient anonymity (UMIN00000516).

Results

Patient Population

A total of 1,551 patients on hemodialysis had been identified by December 31, 2009. In the 3 years after January 1, 2010, 278 patients died, 124 moved to other dialysis facilities, and 21 underwent kidney transplantation (Figure 1). Table 1 shows baseline patient characteristics according to developed CI or not. Eighty-four HD patients developed CI during the 3-year follow-up, with an incidence of 21.5/1000 patients per year. Significant differences were observed in basal renal diseases (DM), age, AF, and a previous history of CI between both groups. No significant difference was observed in antiplatelet/coagulant drug use between the 2 groups.

The number of CI events (n=18) was markedly higher in patients with a previous history of CI (n=147) than in those without (Kaplan-Meier analysis, log-rank test, $p<0.001$) (Figure 2). Cox's regression analysis on patients excluding those with a previous history of CI revealed that the presence of AF (HR 2.879, 95% C.I. 1.508-5.499), age (HR 1.172, 95% C.I. 1.031-1.333), and diabetes mellitus (HR 1.832, 95% C.I. 1.051-3.193) were predictive factors of CI, whereas anticoagulation and antiplatelet therapies were not (Table 2).

On the other hand, 18 out of the 158 patients with AF and 66 out of the 1,393 patients without AF developed CI. A Kaplan-Meier analysis revealed that CI events were significantly more common in patients with AF than in those without (log-rank test, $P<0.001$) (Figure 3A). Among the patients with AF, 5 out of the 34 patients that received warfarin and 13 out of the 124 patients that did not developed CI. No significant difference was observed in the frequency of CI events between warfarin users and non-users (Kaplan-Meier analysis, log-rank test, $P=0.574$) (Figure 3B).

Among the patients with AF, 3 (1 cerebral hemorrhage and 2 gastrointestinal bleeding) out of the 34 patients that received warfarin and 6 (6 cerebral hemorrhage and none gastrointestinal bleeding) out of the 124 patients that did not required hospitalization with major bleeding. No significant difference was observed in the frequency of major bleeding

Table 1. Baseline patient characteristics

	Number missing	Analysis cohort (n=1551)	No CI (n=1467)	Developed CI (n=84)	p value*
Age (yr)	0	69.0 (59.0-78.0)	68.0 (59.0-77.0)	73.0 (66.5-80.5)	<0.001
Female, n (%)	0	643 (41.5)	606 (41.3)	37 (44.0)	0.620
Duration of HD (month)	22	74 (32-143)	75 (32-145)	59 (32.3-116)	0.207
Cause of ESRD (DM), n (%)	0	373 (24.0)	345 (23.5)	28 (33.3)	0.041
Smoker, n (%)	0	249 (16.1)	241 (16.4)	8 (9.5)	0.094
Pre-HD SBP (mmHg)	79	155.3 (143.3-166.9)	155.3 (142.5-167.1)	157.3 (147.1-167.5)	0.224
Pre-HD DBP (mmHg)	88	76.0 (70.0-83.3)	76.0 (69.3-82.7)	76.0 (70.5-81.5)	0.961
Hypertension (pre-HD SBP>180mmHg)	79	151 (9.7)	138 (9.4)	13 (15.5)	0.112
AF, n (%)	0	158 (10.2)	140 (9.5)	18 (21.4)	<0.001
Previous history of CI, n (%)	0	147 (9.5)	129 (8.8)	18 (21.4)	<0.001
Antiplatelet/coagulant drug use					
Antiplatelet only, n(%)	0	484 (31.2)	451 (30.7)	33 (39.3)	0.100
Warfarin only, n (%)	0	37 (2.4)	34 (2.3)	3 (3.6)	0.464
Antiplatelet and warfarin, n (%)	0	35 (2.3)	31 (2.1)	4 (4.8)	0.112
Hemoglobin	144	10.6 (9.7-11.4)	10.6 (9.7-11.4)	10.6 (9.7-11.2)	0.402
Serum total protein	387	6.6 (6.3-6.9)	6.6 (6.3-6.9)	6.6 (6.4-6.9)	0.583
Serum albumin	262	3.8 (3.6-4.0)	3.8 (3.6-4.1)	3.7 (3.5-3.9)	0.015
Serum blood urea nitrogen	94	66.1 (55.9-77.8)	66.3 (56.0-77.8)	63.2 (51.7-77.3)	0.068
Serum creatinine	94	10.6 (8.9-12.5)	10.7 (8.9-12.6)	9.7 (8.4-11.2)	<0.001
Serum uremic acid	95	7.7 (6.9-8.6)	7.7 (6.9-8.6)	7.4 (6.6-8.4)	0.151
Serum total cholesterol	491	155 (134-177)	155 (134-177)	155 (134-170)	0.726
Serum LDL-cholesterol	932	80 (66-99)	80 (66-98)	83 (58-111)	0.431
Serum triglyceride	273	89 (64-122)	89 (64-122)	80 (58-119)	0.361
Serum C-reactive protein	374	0.10 (0.05-0.40)	0.10 (0.05-0.39)	0.20 (0.10-0.46)	0.025
Serum intact parathormone	666	146 (72-245)	148 (73-249)	148 (73-249)	0.032
Serum adjusted Calcium	109	9.0 (8.5-9.5)	9.0 (8.5-9.5)	9.0 (8.3-9.5)	0.667
Serum phosphorus	109	5.2 (4.3-6.0)	5.2 (4.3-6.0)	5.2 (4.1-6.0)	0.558

Continuous variables represented as median with interquartile range in parentheses. *CI free vs developed CI by the $\chi 2$ test or Mann-Whitney test. Abbreviations: SD - standard deviation, ESRD – end-stage renal disease, DM - diabetes mellitus, HD - hemodialysis, SBP - systolic blood pressure, DBP - diastolic blood pressure, AF - atrial fibrillation, CI - cerebral infarction.

events between warfarin users and non-users (Kaplan-Meier analysis, log-rank test, P=0.395).

Discussion

CI events are more common in dialysis patients than in the general population; however, the relationship between CI events and antiplatelet/anticoagulation therapies has not yet been elucidated in dialysis patients. This 3-year cohort study revealed that a previous history of CI is associated with recurrence, while AF is associated with an increased risk of CI in dialysis patients as well as

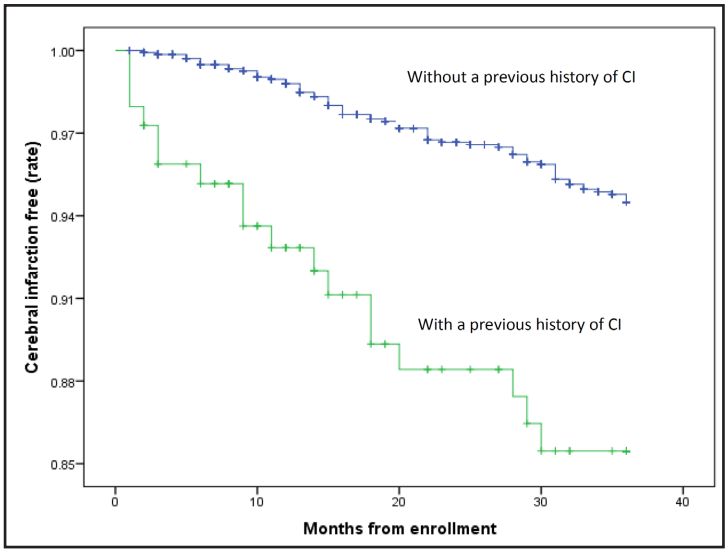

Fig. 2. CI free rates among patients receiving hemodialysis with or without a previous history of CI (Kaplan–Meier analysis). Eighteen out of 147 patients with and 66 out of 1,404 patients without a previous history of CI developed CI events. The incidence of CI events was significantly higher in patients with a previous history of CI than in those without (Log rank test: p<0.001).

in the general population, whereas the benefits of antiplatelet/coagulant usage on the onset of CI was not evident in patients with or without AF. Furthermore, age and the complications associated with diabetes mellitus were identified as risk factors for new CI.

In the present study, no significant difference was observed in antiplatelet/coagulant usage in the groups with and without new CI, and the preventive effects of these drugs on new CI were obscure.

The effectiveness of antiplatelet and anticoagulation therapy for the prevention of cardiovascular diseases [10, 11] and cardiogenic cerebral embolisms associated with AF [9], respectively, has been established in the general population.

Table 2. New CI adjusted hazard risk (AHR) in patients excluding those with a previous history of CI (Cox's regression analysis)

	AHR	95 % CI		P value
Antiplatelet drug only (vs none)	1.444	0.413	-5.056	0.565
Warfarin only (vs none)	1.284	0.740	-2.230	0.374
Combination therapy*	2.143	0.635	-7.237	0.220
Age (/10years)	1.172	1.031	-1.333	0.015
Male	1.031	0.620	-1.715	0.905
Cause of ESRD (DM)	1.832	1.051	-3.193	0.033
Smoker	0.364	0.129	-1.026	0.056
Pre-HD SBP >180mmHg	1.411	0.680	-2.929	0.355
HD duration <74 months (vs ≧74)	0.756	0.442	-1.294	0.308
AF	2.879	1.508	-5.499	0.001

* Combination therapy with antiplatelet drugs and warfarin (vs none).
Abbreviations: ESRD – end-stage renal disease, DM - diabetes mellitus, HD - hemodialysis, SBP - systolic blood pressure, AF - atrial fibrillation.

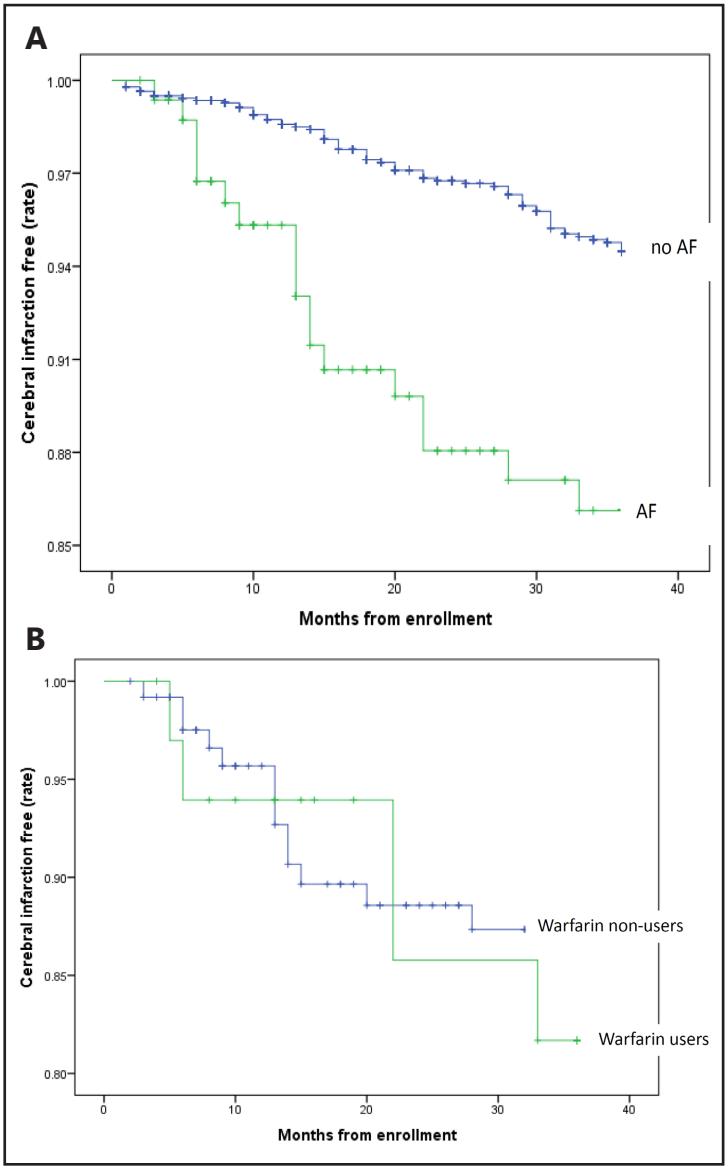

Fig. 3. CI free rates among patients receiving hemodialysis with or without atrial fibrillation (AF) (Kaplan–Meier analysis). Eighteen out of 158 patients with and 66 out of 1,393 patients without AF developed CI. The incidence of CI events was significantly higher in patients with AF than in those without (Log rank test: p<0.001) (Fig. 3A). Five out of the 34 patients with AF that received warfarin and 13 of the 124 patients that did not developed CI events. No significant difference was observed in the frequency of CI events between warfarin users and non-users (Kaplan-Meier analysis, log-rank test, P=0.574) (Fig. 3B).

Furthermore, anticoagulation plus antiplatelet agents are widely used and represent efficient prophylaxis for acute coronary disease [12, 18-20].

Ethier J, et al. [21] examined the patterns and benefits of aspirin in 28,320 hemodialysis patients randomly selected from the Dialysis Outcomes and Practice Patterns Study (DOPPS). The prevalence of aspirin prescriptions varied widely between countries, from 8% (Japan) to 40% (Australia & New Zealand) of patients. Aspirin prescriptions reduced the risk of stroke (relative risk [RR], 0.82; P = 0.03), and no relationship was found between aspirin prescriptions and gastrointestinal bleeding. In addition, a recent large observational study showed that antiplatelet therapy was a safe and effective treatment for the prevention of recurrent ischemic stroke in patients with end-stage renal disease undergoing dialysis [22]. Furthermore, a systemic review of the literature revealed that the use of a single antiplatelet agent did not appear to increase the risk of bleeding [23]. Since hemodialysis patients are also prone to thrombotic complications such as vascular access clotting, antiplatelet agents are recommended for the primary and secondary prevention of these thrombotic events [24]. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative clinical practice guidelines (NKF KDOQI Guidelines) of 2005 indicated that antiplatelet drugs and warfarin may be useful for preventing cardiovascular diseases among end-stage renal disease patients [25]. In the present study, the number of patients with a background that causes CI events may have been higher in the antiplatelet agent group than in the non-antiplatelet agent group: however, no relationship was noted between the usage of antiplatelet agents and CI events in the analysis, excluding patients with a history of CI. In addition, the absence of a relationship between antiplatelet drugs and CI events may be attributed to the small sample size and possibility of aspirin resistance [26, 27].

The incidence and prevalence of AF are higher in dialysis patients than in the general population, and AF is also associated with an increased risk of stroke and mortality in dialysis patients [6, 11, 15]. Sánchez-Perales C, et al. [28] and Clase CM, et al. [29] reported that prophylactic anticoagulation therapy may need to be considered for dialysis patients with AF as well as the general population. In the present study, CI events were significantly more common in patients with AF than in those without; however, no significant difference was observed in the frequency of CI events between patients with AF receiving warfarin and those who did not. The reason for this result may be related to the small number of patients (n=158) and short follow-up periods. However, recent studies also reported that the benefits of anticoagulant therapy for patients with ESRD remain uncertain [30, 31]. The effectiveness and safety of anticoagulation drugs for dialysis patients need to be clarified using a larger number of patients in a prospective randomized control study.

The results obtained in the present study are limited by the short follow-up periods in a relatively small cohort. Furthermore, although the types of antiplatelet agents used and presence or absence of an antiplatelet combination may have influenced the incidence of CI, we did not investigate the types or numbers of antiplatelet drugs. PT-INR and TT were also assessed and managed in the milder range in warfarin users at most facilities, but was not measured in approximately 20% of patients. These limitations may explain why the benefit of therapy with warfarin and/or antiplatelet agents on the onset of cerebral embolism was not observed in dialysis patients with AF.

Conclusion

In summary, CI events were more frequent in dialysis patients with than in those without AF; however, the preventive effects of antiplatelet and/or anticoagulant drugs on the development of CI events were not evident. Randomized trials are warranted in the future in order to determine the benefits and risks of anticoagulation and/or antiplatelet drugs in hemodialysis patients with AF on cerebrovascular events.

Disclosure Statement

None.

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