

Original article

Title:

Association of 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

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.

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 (HR 3.36; 95% CI, 0.94 to 11.23). Similar results were obtained after propensity score matching (HR 3.36; 95% CI, 0.67 to 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.

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 more than 24 hours 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 χ^2 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).

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/m² (SD, 2.9), and median duration on dialysis of 10 years (range, 0 to 38). All patients were dialyzed three times a week for three to five hours.

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 filled a prescription for warfarin and 32 (53%) did 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 and Figure 1A). However, there were too few cases to provide individual HR estimates (95% confidence interval (CI), 0.63 to 5.93). After adjusting for CHADS2 score as a continuous variable, the HR increased (HR, 3.36, 95% CI, 0.94 to 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 to 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 and 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 and 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 to 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 100 person-years (HR 1.00; 95% CI, 0.40 to 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 to 4.96), rather than ischemic (HR 0.92; 95% CI, 0.61 to 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 to 0.74) [11]. However, this study included not 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, other 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]. 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 back 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.

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Figure legends

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.

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).