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Research Paper

Clinical Features and Prognosis in Patients with Atrial Fibrillation and Prior Stroke: Comparing the Fushimi and Darlington AF Registries

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ABSTRACT

Background: Ethnic differences in clinical characteristics, stroke risk profiles and outcomes among atrial fibrillation (AF) patients may exist. We therefore compared AF patients with previous stroke from Japan and the United Kingdom (UK).

Methods: We compared clinical characteristics, stroke risk and outcomes among AF patients from the Fushimi AF registry who had experienced a previous stroke (Japan; $n = 688$; 19.7%) and the Darlington AF registry (UK; $n = 428$; 19.0%).

Results: AF patients with previous stroke in Fushimi were significantly younger (76.8 and 79.6 years of age in Fushimi and Darlington; $p < 0.01$) with a lower proportion of females (37.4% vs. 45.1%; $p = 0.01$) than those from Darlington. Although the CHA_2DS_2-VASc score was lower in AF patients in Fushimi than those in Darlington (5.18 vs. 5.57; $p < 0.01$), oral anticoagulation (OAC) was prescribed significantly more frequently in Fushimi (68.3%) than Darlington (61.7%) ($p = 0.02$). Multivariate logistic regression analysis showed that Japanese ethnicity was associated with a significantly decreased risk of recurrent stroke (OR 0.59. 95% CI 0.36–0.97; $p = 0.04$) but a significantly increased risk of all-cause mortality (OR 1.76, 95% CI 1.18–2.66; $p < 0.01$) in AF patients with previous stroke.

Conclusions: AF patients with previous stroke in the UK were at higher risk of recurrent stroke compared to Japanese patients, but OAC was utilised less frequently. There was a lower risk of recurrent stroke in the secondary prevention cohort from the Fushimi registry, but an increased risk of all-cause mortality.

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1. Introduction

Atrial fibrillation (AF) patients are at the increased risk of ischemic stroke and death (Kopecky et al., 1987; Wolf et al., 1991). Of the various risk factors, previous stroke or transient ischemic attach (TIA) are the most powerful risk factors for subsequent ischemic stroke and confer a significant risk of mortality and recurrent stroke, approximately 12% per year, if left untreated (Stroke Risk in Atrial Fibrillation Working Group, 2007). Indeed, AF-related ischemic strokes are generally more disabling and more often life-threatening than other types of stroke (Marini et al., 2005). Thus, secondary prevention with oral anticoagulant (OAC) is crucial for AF patients with previous stroke EAFT (European Atrial Fibrillation Trial) Study Group (1993). However, little is known about possible differences in the clinical characteristics, practices and outcomes between AF patients with previous stroke in Japan compared to their British counterparts.

In this study, we used individual-level patient data from the Fushimi AF registry and the Darlington AF registry to assess differences in clinical characteristics, stroke risk profiles and outcomes among AF patients with previous stroke or TIA.

2. Materials and Methods

The details of the study designs, patient enrolment, definitions used, and baseline patient clinical characteristics of the Fushimi AF registry (UMIN Clinical Trials Registry: UMIN000005834) and the Darlington

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AF registry have been previously described (Akao et al., 2013; Shantsila et al., 2015).

2.1. Fushimi AF Registry

The Fushimi AF registry is a prospective, observational registry intended to identify the current status of AF patients in a community-based clinical setting in Fushimi-ku, Kyoto, Japan (Akao et al., 2013). Fushimi-ku is an urban administrative district in the southern area of the city of Kyoto, with a total population of 284,000 (Japanese were >99%) in 2011. The enrolment of patients with AF documented on a 12-lead electrocardiogram (ECG) or Holter monitoring at any time (with no exclusion criteria) commenced in March 2011. Eighty institutions (all members of Fushimi-Ishikai (Fushimi Medical Association)) participated in this registry and attempted to enroll all consecutive AF patients under regular outpatient care or under admission. Follow-up data was collected annually through review of the inpatient and outpatient medical records, and contact with patients, relatives and/or referring physicians by mail or telephone. The study protocol was approved by the ethical committees of the National Hospital Organization Kyoto Medical Center and Ijinkai Takeda General Hospital.

2.2. Darlington AF Registry

The study population of the Darlington AF registry was derived from all 105,000 patients who were registered at one of 11 general practices serving the town of Darlington, UK (Shantsila et al., 2015), a market town, with a resident population of 106,000 in 2011. According to the last Census data in the Darlington cohort, >96% of population were White Caucasian in Darlington. All patients with a history of AF or atrial flutter whose vital status in March 2013 was known, were eligible for inclusion. Demographic and clinical data were collected from electronic GP records (followup is still ongoing as part of routine clinical care in this contemporary primary care population) including stroke risk factors and antithrombotic treatment (Cowan et al., 2013; Shantsila et al., 2015).

In the present study, we used the data from all the AF patients in the Fushimi AF registry ($n = 3499$) and those with follow-up information in the Darlington AF registry ($n = 2259$). We identified those patients who had a history of stroke or TIA ($n = 688$ in Fushimi AF registry; $n = 428$ in Darlington AF registry) and categorized stroke risk using the $CHADS_2$ (Gage et al., 2001) and CHA_2DS_2-VASc scores (Lip et al., 2010). OAC was defined as vitamin K antagonists (predominantly warfarin) and non-vitamin K antagonists (dabigatran, rivaroxaban, apixaban and edoxaban). The primary outcomes of the present study were the incidence of any-cause recurrent stroke and all-cause mortality during the 12-month follow-up period. The secondary outcome was a composite of any-cause stroke and all-cause mortality during the first year.

2.3. Statistical Analysis

Continuous data are presented as mean and standard deviation (SD). The incidence of stroke and all-cause mortality during the one-year follow-up period were calculated as number and percentage. Censoring was done for the first event recorded. We compared categorical variables using the chi-square test and continuous variables using independent samples *t*-test for normally distributed data or Mann-Whitney *U* test for non-normal distribution. The unadjusted odds ratios were determined using logistic regression for each risk profile. The predictive accuracy of $CHADS_2$ and CHA_2DS_2-VASc scores for the study subjects was determined using receiver-operator characteristic curves. Finally, to determine independent risk factors for stroke and all-cause mortality, we carried out multivariate logistic regression using age, sex, congestive heart failure, hypertension, diabetes mellitus (DM), vascular disease and OAC prescription at baseline as co-varieties. These analyses were performed using JMP version 12.2.0 (SAS Institute, Cary, NC). Statistical significance was set as a two-sided *p*-value of <0.05.

3. Results

The analyses included 1116 AF patients with history of stroke or TIA at baseline (Fushimi AF registry, $n = 688$; Darlington AF registry, $n = 428$). The secondary prevention AF patients in the Fushimi registry were significantly younger, with fewer females and less likely to have hypertension and vascular disease, compared with those in the Darlington registry (Table 1).

Mean $CHADS_2$ and CHA_2DS_2-VASc scores were significantly lower in Fushimi registry patients. The distribution of age group is shown in Table 1. The proportion of elderly patients was higher in the Darlington registry with >70% age ≥ 75 years; 17 (2.5%) patients in Fushimi and 18 (4.2%) patients in Darlington were aged ≥95 years. Patients with $CHADS_2$ score ≤ 3 were more frequent in Fushimi significantly ($p = 0.004$) (Fig. 1A and B), while patients with a CHA_2DS_2-VASc score ≥ 6 were significantly more common in the Darlington cohort ($p < 0.001$).

3.1. Antithrombotic Drug Use in Both Registries

OAC was prescribed more often in the Fushimi cohort than the Darlington cohort (68.3% vs. 61.7%; $p = 0.023$) (Table 1). The prescription of vitamin K antagonist (VKA, predominantly warfarin) was comparable (62.5% vs. 60.1%; $p = 0.413$), but prescription of non-vitamin K oral anticoagulants (NOAC) was significantly higher in Japan than in the UK (5.8% vs. 1.6%). The prescription of anti-platelet therapy drugs (APT), including monotherapy or as combination therapy, was comparable (39.7% vs. 40.9%; $p = 0.689$), with concomitant use of OAC and APT being significantly more frequent in the Fushimi cohort (23.3% vs. 9.1%), in all age groups and CHA_2DS_2-VASc scores. Fig. 2 shows the prescription of antithrombotic therapy according to age (Fig. 2A) and CHA_2DS_2-VASc score (Fig. 2B).

In Darlington, the age 85+ group had a higher rate of OAC and AP use than all other age subgroups.

3.2. Study Outcomes

During one-year of follow-up, stroke occurred in 33 (4.8%) and 37 (8.6%) patients in the Fushimi and Darlington cohorts, respectively

Table 1
Patient characteristics and medication of the secondary stroke prevention cohort at baseline.

Number (%)	Fushimi AF registry (Japan) ($n = 688$)	Darlington AF registry (UK) ($n = 428$)	*p* value
Mean age (SD), years	76.8 (9.5)	79.6 (9.6)	<0.001
Age < 65 years	70 (10.2)	28 (6.5)	0.002
Age 65–74 years	194 (28.2)	93 (21.7)	
Age ≥ 75 years	424 (61.6)	307 (71.7)	
Female gender	257 (37.4)	193 (45.1)	0.010
Heart failure	191 (27.8)	106 (24.8)	0.271
Hypertension	443 (64.4)	305 (71.3)	0.018
Diabetes mellitus	169 (24.6)	120 (28.0)	0.198
Vascular disease	85 (12.4)	97 (22.7)	<0.001
Mean $CHADS_2$ score (SD)	3.78 (0.97)	3.96 (0.94)	0.003
Mean CHA_2DS_2-VASc score (SD)	5.18 (1.34)	5.57 (1.27)	<0.001
Medication			
OAC	470 (68.3)	264 (61.7)	0.023
Vitamin K antagonist	430 (62.5)	257 (60.1)	0.413
Non-vitamin K antagonist	40 (5.8)	7 (1.6)	0.001
Anti-platelet drugs	273 (39.7)	175 (40.9)	0.689
Concomitant use of OACs and anti-platelet drugs	160 (23.3)	39 (9.1)	<0.001

AF: atrial fibrillation, OAC: oral anticoagulants; UK: United Kingdom.

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