Multicenter Prospective Analysis of Stroke Patients Taking Oral Anticoagulants: The PASTA Registry - Study Design and Characteristics

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Objectives: The management of atrial fibrillation and deep venous thrombosis has evolved with the development of direct oral anticoagulants (DOAC), and oral anticoagulant (OAC) might influence the development or clinical course in both ischemic and hemorrhagic stroke. However, detailed data on the differences between the effects of the prior prescription of warfarin and DOAC on the clinical characteristics, neuroradiologic findings, and outcome of stroke are limited. *Design:* The prospective analysis of stroke patients taking anticoagulants (PASTA) registry study is an observational, multicenter, prospective registry of stroke (ischemic stroke,

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Received July 31, 2019; revision received August 30, 2019; accepted September 27, 2019.

Funding: This research was supported by Nippon Boehringer Ingelheim Co. Ltd.

Trial registration: UMIN000030877

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1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2019.104456

transient ischemic attack, and intracerebral hemorrhage) patients receiving OAC in Japan. This study is designed to collect data on clinical background characteristics, drug adherence, drug dosage, neurological severity at admission and discharge, infarct or hematoma size, acute therapy including recanalization therapy or reverse drug therapy, and timing of OAC re-initiation. Patient enrollment started in April 2016 and the target patient number is 1000 patients. *Conclusions:* The PASTA prospective registry should identify the status of stroke patients taking OAC in the current clinical practice in Japan.

Key Words: Atrial fibrillation—direct oral anticoagulant—oral anticoagulants—stroke—warfarin

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is known to increase the risk of ischemic stroke (IS) and mortality. The number of patients with AF is steadily increasing in Japan, and it is estimated that 1 million people will have AF by 2020-2030 due to the aging of the population.[1,2] The concept and tools of oral anticoagulant (OAC) therapy for preventing stroke in patients with nonvalvular atrial fibrillation (NVAF) and deep venous thrombosis have changed in the past 10 years. Direct OAC (DOAC) was approved in Japan in 2011, thereby, increasing anticoagulation therapy options for patients with NVAF or deep venous thrombosis. Because DOACs are theoretically more suitable than warfarin for these patients, they are used liberally in clinical practice.[3] An increasing number of patients with poor adherence and/or inappropriate low-dose therapy of DOACs have experienced IS or intracerebral hemorrhage (ICH), negatively affecting prognosis.[4,5] However, the clinical outcomes of current anticoagulant treatment in stroke patients have not been fully investigated.

An analysis of 5 pooled trials (MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND IA) reported in 2015 established the superiority of endovascular thrombectomy (EVT) to best medical management in patients with anterior circulation large-vessel occlusion.[6] Subsequently, the number of patients treated with EVT started increasing notably.[5] However, the safety of EVT in patients receiving DOAC have not been fully investigated. Moreover, reversal agents such as idarucizumab have been available for dabigatran-related bleeding since 2016 and four-factor prothrombin complex concentrate has been available for warfarin-related bleeding since 2017 in Japan.[7,8] These major changes should have influenced the characteristics and outcomes in stroke patients taking OAC. However, available data are limited to small retrospective studies without detailed analyses of the differences between warfarin and DOAC.

The present prospective multicenter study aims to clarify the clinical background, adherence, inappropriate OAC treatment, neuroradiological characteristics, acute therapy, management including OAC re-initiation after event, and outcome in patients with IS, transient ischemic attack (TIA), and ICH during therapy with OAC in clinical practice.

Methods

Study Design

The PASTA registry is an observational, multicenter, prospective registry of patients with TIA, IS, and ICH who are taking OAC (warfarin or DOAC), or suspending OAC within 7 days. Patient enrollment started in April 2016 in 25 medical institutions throughout Japan. Ethical approval was obtained from the Nippon Medical School ethics review committee and the relevant ethics committees at all participating sites. Written informed consent is required from all participants or participant family members prior to study participation. The study is being conducted in accordance with the ethical principles of the Declaration of Helsinki. The trial is registered with the UMIN-clinical trials registry (registration number: UMIN000030877).

Subjects

The inclusion criteria for this study are as follows: (1) patients with IS, TIA, or ICH who have been prescribed warfarin or DOAC (dabigatran, rivaroxaban, apixaban, and edoxaban) or OAC, within 7 days before inclusion; (2) those who were hospitalized or visited the hospital as an outpatient within 7 days of onset; and (3) patient, family, or other representative consent to participate in the study. We do not register intracranial hemorrhages such as subarachnoid hemorrhage, acute or chronic subdural hematoma, and epidural hematoma except for ICH. Our previous study reported that more than 10% of all stroke patients receive OAC.(4) Therefore, the estimated total number of recruited patients for this study will be 1000 in 3 years.

Evaluations and Follow-up

Table 1 shows the protocol schedule of the present study. Patients are evaluated at baseline for clinical background characteristics, including sex, age, premorbid modified Rankin scale (mRS) score, prestroke $CHADS_2$

score, CHA_2DS_2-VASc score or HAS-BLED score, blood glucose level, creatinine clearance, coagulation test including international normalized ratio (INR) and activated partial thromboplastin time, and DOAC dose. In addition, the presence of prestroke dementia, drug adherence, last medication time, and prestroke blood pressure control levels are recorded. Insufficient treatment with warfarin (corresponding to warfarin treatment and a prothrombin time-INR [PT-INR] on admission of less than 2.0 for patients aged less than 70 years and PT-INR less than 1.6 for patients aged ≥70 years) is determined based on previous studies in Japan and on domestic guidelines.[9,10] Adherence to OACs is assessed using the following questions: Do you ever forget to take your medicine? If yes, how many times a week do you forget to take your medicine? Inappropriately lowered dose of DOAC is defined as administration of low-dose DOAC despite the standard dosage criteria being met based on our domestic label (Table 2). Dabigatran does not have definite dose reduction criteria, but reduction is recommended for any 1 of the following: age ≥70 years, creatinine clearance 30-50 mL/min, history of major bleeding, and use of p-glycoprotein inhibitors. We defined a nonrecommended low dose of dabigatran as an inappropriately lowered dose for statistical analysis in the present study. Stroke severity is assessed using the National Institutes of Health Stroke Scale (NIHSS) score on admission and mRS at discharge. If recanalization therapy is performed, including intravenous thrombolysis and/or endovascular therapy, we collect the data of hemorrhagic transformation within 36 hours after recanalization therapy, and the interval from the last OAC intake time to recanalization time. We also record days from event onset to restarting anticoagulant therapy.

Study Organization and Funding

The PASTA study was organized by a central coordinating center located at the Department of Neurology, Nippon Medical School, and is being conducted at 25 centers, located in Japan. The steering committee is managing the trial. The PASTA study received funding support from Nippon Boehringer Ingelheim Co. Ltd.

Statistical Analysis

All registered participants in the PASTA study will be included in the analyses. The current status of adherence and inappropriate OAC dosage, patient characteristics, medical history, concomitant use of antiplatelet agents, vital signs, laboratory and urine data, initial NIHSS score, neuroimaging characteristics, mRS score at discharge, and mortality during hospitalization or at the restart of treatment with OAC will be compared between those taking DOAC and those taking warfarin. Data will be presented as the median (interquartile range) for continuous data or as a number (%) for categorical data. Intergroup differences will be assessed using the chi-square test or the Wilcoxon rank-sum test, as appropriate. Multivariate logistic

Table 1. *Study schedule*

Variable	Pre-event	At admission	36 h after event	During hospitalization	At discharge
Anticoagulant status prior to the event	✔				
Anticoagulant adherence	✔				
Concomitant with antiplatelet use	✔				
Heparin bridging	✔				
Prior blood pressure control level	✔				
Dementia	✔				
Vascular risk factors	✔				
$CHADS_2$ score	✔				
CHA_2DS_2-VASc score	✔				
HAS-BLED score	✔				
mRS	✔				✔
NIHSS score		✔			
Blood and urinary examination		✔			
Acute treatment		✔			
Reperfusion therapy		✔			
Reversal agents		✔			
Neuroimaging		✔	✔		
Echocardiogram				✔	
Secondary prevention				✔	
Timing				✔	
Drug choice				✔	
Throboembolic event				✔	
Hemorrahagic complication				✔	

Abbreviations: DOAC, direct oral anticoagulant; mRS, modified Rankin Scale; NIHSS, National Institutes of Health stroke scale.

Table 2. *DOAC dose reduction criteria in patients with NVAF in Japan*

Dabigatran (standard 150 mg BID and lowered 110 mg BID), with any one of the following (recommended):
Age ≥ 70 y
Ccr ≤ 50 ml/min
History of gastrointestinal bleeding
Concomitant use of P-glycoprotein inhibitor
Rivaroxaban (standard 15 mg QD and lowered 10 mg QD), Ccr ≤ 50 mL/min
Apixaban (standard 5 mg BID and lowered 2.5 mg BID), with more than one of the following:
Age ≥ 80 y
Body weight ≤ 60 kg
Serum creatinine ≥ 1.5 mg/dl
Edoxaban (standard 60 mg QD and lowered 30 mg QD), with any 1 of the following:
Body weight ≤ 60 kg
Ccr ≤ 50 ml/min
Concomitant use of quinidine, verapamil, erythromycin, or cyclosporine

Abbreviations: BID, twice daily; Ccr, creatinine clearance; DOAC, direct oral anticoagulant; NVAF, nonvalvular atrial fibrillation; QD, once daily.

regression model analysis will be performed to identify variables independently associated with mild neurological severity at admission (NIHSS score ≤ 10) and poor discharge outcome (mRS ≥ 3). All analyses will be performed using JMP version 13 (SAS Institute Inc., Cary, NC), with a value of $P < .05$ indicating statistical significance.

Discussion

Because of the aging population in Japan, and because DOACs are used liberally in clinical practice, we expect that the incidence of IS/ICH related to DOAC will increase in coming years. Some researchers have reported characteristics or outcomes in patients with IS/TIA and ICH during OAC therapy in clinical practice, but most of these studies were retrospective, single-center, and with small case numbers. Therefore, we planned to recruit patients prospectively and to compare the characteristics and outcomes of IS/TIA/ICH patients already receiving DOAC and warfarin treatment in clinical practice in Japan.

Sufficient warfarin therapy has been reported to reduce stroke severity and improve clinical outcomes when patients with AF suffer IS, compared with those on no OAC.[11,12] DOAC therapy has been shown to reduce the risk of IS as well as well-controlled warfarin in patients with NVAF.[13-16] Therefore, theoretically, appropriate doses of DOACs would also have the potential, at least as well as warfarin, to reduce the initial severity of IS when patients taking DOACs suffer stroke.[17] Some retrospective studies reported that prior DOAC therapy (n = 57) was associated with mild IS at admission and with a low frequency of large vessel occlusion.[5,18] However, the effect of DOAC therapy on initial severity and outcome after IS has not been fully investigated prospectively. Furthermore, the impact of adherence and/or inappropriate dose of DOACs, which could affect patient outcomes, has not been established.[19,20]

The number of patients treated with EVT for large vessel occlusion is notably increasing.[5] However, the safety of recanalization therapy including EVT in patients receiving DOAC has not been fully investigated.[21] All 4 major DOAC trials excluded NVAF patients within 7-30 days after stroke onset, and it was not possible to obtain any data regarding the safety and efficacy of DOAC for immediate anticoagulation from the trials.[13-16] The efficacy and safety of the re-initiation of OAC for acute IS patients with NVAF have not been well examined. The PASTA study will identify the current status and safety of EVT during OAC therapy and the timing of re-initiation of OAC in acute IS patients with AF.

ICH has occurred less frequently in patients treated with DOACs than in those treated with warfarin in clinical trials.[7-10] Therefore, DOACs also have the potential, like warfarin, to reduce the initial severity of ICH. The relationship between prior DOAC prescription and ICH characteristics has not been determined. Some retrospective studies have reported that DOAC-related ICH is associated with a lower hematoma volume and better clinical outcomes than warfarin-related ICH.[22-24] Recently, a nationwide study using the Diagnosis Procedure Combination database in Japan revealed that DOAC-treated patients experienced less severe ICH and lower mortality rates than warfarin-treated patients.[25] Conversely, another prospective observational study reported that DOAC-related ICH (n = 61) is associated with high mortality and an unfavorable outcome, and hematoma expansion is frequent.[26] The PASTA registry will identify the differences in neurological severity, neuroimaging characteristics (hematoma location, hematoma expansion, and the association between cerebral microbleeds and hematoma), functional outcome between DOAC (standard dose, appropriate low dose, and inappropriate low dose) and warfarin (sufficient and insufficient control). Moreover, PASTA study will identify the current status and safety for acute treatment including OAC reversal agent and the timing of re-initiation of OAC in acute ICH.

Summary and Conclusion

Although 4 major DOAC clinical trials featured very strict inclusion criteria, their results cannot be generalized to all stroke patients receiving DOAC. Notably, in the clinical practice of stroke prevention in AF, stroke outcomes can depend on various patient baseline characteristics, suboptimal dosage, OAC therapy adherence, and concomitant use of antiplatelet therapy, etc. Moreover, EVT and OAC reversal agents are developing. The PASTA prospective multicenter registry study will identify the current status of stroke patients taking OAC in real-world settings.

Declaration of Competing Interest

Satoshi Suda received lecture fees from Daiichi Sankyo Co. Ltd. Yasuyuki Iguchi received lecture fees from Bayer Healthcare Co. Ltd. and Daiichi Sankyo Co. Ltd. Shigeru Fujimoto received lecture fees from Nippon Boehringer Ingelheim Co. Ltd. and Daiichi Sankyo Co. Ltd. Yu Kono received research funding from Sanofi Co. Ltd. Takao Kanzawa received lecture fees from Daiichi Sankyo Co. Ltd. Kazumi Kimura received lecture fees from Bristol-Myers Squibb Co. Ltd., Nippon Boehringer Ingelheim Co. Ltd., Bayer Healthcare Co. Ltd., and Daiichi Sankyo Co. Ltd, and research funding from Nippon Boehringer Ingelheim Co. Ltd. and Daiichi Sankyo Co. Ltd.

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