Original article

# Comparative effectiveness and safety of warfarin and dabigatran in patients with non-valvular atrial fibrillation in Japan: A claims database analysis

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## ARTICLE INFO

## ABSTRACT

*Background:* Antithrombotic therapy, including direct oral anticoagulants, is recommended in patients with non-valvular atrial fibrillation (NVAF) who are at intermediate-to-high risk of stroke. The aims of this study were to assess the patterns of oral anticoagulant (OAC) prescription in Japanese patients with NVAF and compare the effectiveness and safety of dabigatran and warfarin.

*Methods:* This was a retrospective observational study of adults with NVAF who initiated dabigatran or warfarin between March 14, 2011 and June 30, 2016, using electronic claims data of approximately 12.94 million patients from 230 hospitals. Propensity score matching was used to derive equal patient cohorts. Outcomes included the combined incidence of stroke, systemic embolism, and intracranial bleeding (primary endpoint) and the incidence of major bleeding (secondary endpoint).

*Results:* Overall, 400,884 patients were included. Among those prescribed an OAC, warfarin was the most common (34.3%). For the comparison of dabigatran and warfarin, 4606 patients were propensity-score matched in each cohort. Dabigatran recipients had lower incidences of stroke, systemic embolism, and intracranial bleeding [29.0 vs. 35.6 per 1000 patient-years; hazard ratio (HR), 0.72; 95% confidence interval (CI): 0.53–0.97; $p = 0.031$] and major bleeding (6.4 vs. 11.3 per 1000 patient-years; HR, 0.55; 95% CI: 0.30–0.99; $p = 0.048$). The most common type of bleeding in both groups was gastrointestinal and the incidence was lower in dabigatran recipients (1.6 vs. 6.4 per 1000 patient-years; HR, 0.24; 95% CI: 0.08–0.69; $p = 0.009$).

*Conclusions:* In Japan, dabigatran was associated with a lower risk of stroke, systemic embolism, and intracranial bleeding and major bleeding compared with warfarin in patients with NVAF.

## Introduction

The incidence of atrial fibrillation (AF) is highly dependent on age [1], and, as the population of Japan rapidly ages [2], more than a million people are expected to have AF by the year 2050 [3].

Dabigatran was the first direct oral anticoagulant approved for stroke prevention in patients with non-valvular atrial fibrillation (NVAF). The RELY (Randomized Evaluation of Long-term Anti-coagulation Therapy) study evaluated the benefits and risks of dabigatran compared with those of warfarin in 18,113 patients with NVAF [4]. The results showed that, compared with warfarin, dabigatran 110 mg was associated with similar rates of stroke and systemic embolism and lower rates of major hemorrhage. Compared with warfarin, dabigatran 150 mg was associated with lower rates of stroke and systemic embolism, but similar rates of

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major hemorrhage. The RELY study included only 326 Japanese patients and was insufficiently powered to demonstrate significant efficacy of dabigatran in this population [5]. In addition, the effectiveness and safety of dabigatran and warfarin were compared in real-world studies conducted in the USA, Japan, and Taiwan [6–8]. In these studies, dabigatran reduced the risk of ischemic stroke, intracranial hemorrhage, and death [6,7], and was associated with significantly less major bleeding than warfarin [8]. In a comparative safety study using Japanese administrative databases, rates of hospitalized bleeding were also found to be lower in dabigatran- compared with warfarin-treated patients [9]. Interim findings of a post-marketing surveillance study of dabigatran in Japan further support its long-term use in patients with NVAF [10].

The aim of this study was to utilize real-world data from a hospital information database to assess the effectiveness and safety of dabigatran or warfarin for stroke prevention in Japanese patients with NVAF.

## Materials and methods

This was a retrospective, observational study of data from the hospital information systems and administration database provided by Medical Data Vision (MDV, Tokyo, Japan), which covers more than 12.94 million in- and out-patients treated at 230 acute care hospitals within secondary medical care blocs across Japan. These hospitals used the Diagnosis Procedure Combination (DPC) case-mix classification system for in-patient reimbursement claims. The database contains anonymous information from health insurance claims for out-patients, administrative data for in- and out-patients, prescriptions, operations and medical procedures, hospitalizations, and results of laboratory tests from some of the participating hospitals [11]. The study protocol was reviewed and approved by the Keio University's Faculty of Pharmacy Ethics Committee for Research Involving Humans, which also waived the informed consent requirements, on 11 October 2017 in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects. The study was registered with ClinicalTrials.gov (NCT03254134).

An incident cohort design was used for assessing the effectiveness and safety of dabigatran in comparison with warfarin [12]. The database was searched for adults (age $\geq$18 years) with NVAF (ICD-10 code I48) who had been newly started on dabigatran or warfarin in either the in- or out-patient setting between 14 March 2011 and 30 June 2016. The date of the first oral anticoagulant (OAC) prescription was defined as the index date. Medical records for the preceding 12 months were searched to verify that there were no previous records of an OAC prescription. Patients were excluded if, during the 12 months before the index date, they were: on dialysis or had a kidney transplant; had a diagnosis of atrial flutter, valvular AF, mechanical valve replacement, rheumatic AF or mitral valve prolapse/regurgitation or stenosis; or had a deep vein thrombosis or pulmonary embolism <6 months before the AF diagnosis. These data were used to find the number of patients prescribed each OAC as the first anticoagulant for NVAF. Incident patients were followed from the index date to the day of treatment discontinuation (defined as a treatment gap >14 days after supply of the last prescription); the day before switching to a different anticoagulant; the date of disenrollment from the MDV database; end of the study period; occurrence of an event of interest; or death of the patient, whichever occurred first.

The primary outcome was the composite of stroke, systemic embolism, and intracranial bleeding during follow-up in the matched cohorts of warfarin and dabigatran recipients. Secondary outcome was the incidence of major bleeding events. The definition of stroke, systemic embolism, and intracranial bleeding

used in the present study (Supplementary Table 1) has been validated in previous research using the MDV claims database [13]. The definition of a bleeding event has also been validated previously [14]. Major bleeding was defined as any transfusion and/or any hospitalization with associated bleeding, which was recorded as the medical condition requiring the most healthcare resource during the hospitalization in DPC in-patient claims. Any diagnostic code with a "suspect flag", meaning the diagnosing physician suspects the diagnosis, was excluded from the analysis. Sensitivity analysis was performed using the Gorst-Rasmussen's definition of stroke/systemic embolism (SE) [15]. A post hoc sensitivity analysis was also conducted for major bleeding as defined by Kohsaka and colleagues [9]. The paper was published after the present study protocol was registered on clinicaltrial.gov, thus any analysis using Kohsaka's definitions is post hoc and not included in the original protocol.

### Statistical methods

Sample size calculations were performed before study initiation using the primary outcomes data from a subanalysis of Asian patients who participated in the RELY study [stroke/SE rate of 0.03 per patient-year and a hazard ratio (HR) of 0.716] [16]. The target sample size of the dabigatran group was estimated to be 4,419. With this sample size, there was <10% chance that the upper bound of the 95% confidence interval (CI) of the primary outcome HR would exceed 1.378, the non-inferiority margin applied in the RELY study.

Matched cohorts of patients receiving warfarin and dabigatran were identified using propensity score (PS) matching. Nearest-neighbor matching without replacement was performed at a 1:1 ratio and using a caliper width of 0.10 of the standard deviation of the logit of the propensity score. The initial logistic regression model for PS calculation used all covariates (Supplementary Table 2) except those with less than 10 patients and the $CHADS_2$ score, which showed high co-linearity with the $CHA_2DS_2\text{-}VASc$ score. The robustness of the logistic model for PS matching using the "full" model was tested against the "reduced" model after covariates were selected using a stepwise method. Ultimately, the "full" model was chosen to conduct PS matching. To examine the balance between matched cohorts, the standardized difference was calculated for variables included in the PS calculation (Table 1).

For each treatment group, the mean, 25th, 50th, and 75th percentiles and standard deviation (SD) were calculated for age. In addition, the number and percentage of patients with each baseline characteristic were calculated for each treatment group. Cox regression model was used to estimate the HRs for the outcomes and their CIs. Kaplan–Meier curves were plotted for the events of ischemic stroke and major bleeding.

## Results

Overall, 400,884 patients diagnosed with NVAF between 2011 and 2016 were included in the MDV database, and 22,490 of these patients had dabigatran or warfarin prescribed as the first OAC and had at least 12 months of baseline data prior to the index date. Compared with warfarin, dabigatran was more likely to be prescribed by cardiologists (Table 1). A higher proportion of patients prescribed warfarin (76%) had a history of hospitalization compared with patients receiving dabigatran (49%). The dabigatran group tended to be younger and have lower $CHADS_2$, $CHA_2DS_2\text{-}VASc$, and HAS-BLED scores than the recipients of warfarin (data not shown). The mean follow-up period of dabigatran and warfarin was calculated as 212 and 180 days, respectively. The majority (78%) of patients taking dabigatran were receiving 110 mg twice daily or less and only 21% were receiving 150 mg twice daily.

**Table 1**
Baseline demographic and clinical characteristics before and after propensity score matching.

| | Whole patients | | | After propensity score matching | | |
|---|---|---|---|---|---|---|
| | Dabigatran (n = 5146) | Warfarin (n = 13,115) | Standardized difference | Dabigatran (n = 4606) | Warfarin (n = 4606) | Standardized difference |
| Mean (SD) age, years | 72 (10) | 78 (10) | 0.540 | 74 (10) | 73 (11) | 0.017 |
| Female, % | 33 | 40 | 0.155 | 34 | 34 | 0.003 |
| Oral anticoagulant prescriber, % | | | | | | |
|   Internal medicine physician | 34 | 34 | 0.002 | 35 | 35 | 0.010 |
|   Cardiologist | 29 | 20 | 0.228 | 27 | 27 | 0.000 |
|   Cardiovascular internal medicine | 9 | 10 | 0.040 | 9 | 9 | 0.007 |
|   Neuropathic internal medicine | 4 | 3 | 0.050 | 4 | 4 | 0.006 |
|   Orthopedic surgeon | 2 | 4 | 0.114 | 3 | 3 | 0.004 |
| Medical history, % | | | | | | |
|   Heart failure | 33 | 50 | 0.364 | 35 | 35 | 0.009 |
|   Diabetes mellitus | 28 | 30 | 0.042 | 29 | 29 | 0.002 |
|   Dyslipidemia | 26 | 22 | 0.098 | 26 | 27 | 0.021 |
|   Myocardial infarction | 1 | 2 | 0.041 | 1 | 1 | 0.006 |
|   Stroke or TIA | 13 | 13 | 0.006 | 13 | 13 | 0.004 |
|   Coronary artery disease | 0 | 1 | 0.021 | 0 | 0 | 0.000 |
| Concomitant medication, % | | | | | | |
|   PPI | 38 | 44 | 0.122 | 39 | 40 | 0.014 |
|   H$_2$ receptor antagonist | 15 | 21 | 0.135 | 16 | 17 | 0.011 |
| History of hospitalization, n (%) | 49 | 76 | 0.596 | 54 | 54 | 0.003 |
| Mean (SD) CHADS$_2$ score | 1.9 (1.4) | 2.5 (1.4) | 0.369 | 2.0 (1.4) | 2.1 (1.4) | 0.017 |
| Mean (SD) CHA$_2$DS$_2$-VASc score | 3.2 (1.8) | 3.9 (1.7) | 0.415 | 3.3 (1.7) | 3.3 (1.7) | 0.005 |
| Mean (SD) HAS-BLED score | 2.0 (1.1) | 2.4 (1.1) | 0.308 | 2.1 (1.0) | 2.1 (1.1) | 0.002 |

CHA$_2$DS$_2$-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes, stroke, vascular disease, age 65–74 years, sex; CHADS$_2$, congestive heart failure, hypertension, age ≥75 years, diabetes, stroke; HAS-BLED, hypertension, abnormal renal and liver function, stroke, bleeding, labile international normalized ratio, elderly, drugs or alcohol; PPI, proton pump inhibitor; SD, standard deviation; TIA, transient ischemic attack.

### Propensity score matching

The "full" all-inclusive model and the "reduced" stepwise model for PS calculation produced similar goodness-of-fit statistics, such as Akaike information criterion (19,148.328 vs. 19,128.694,

respectively), C-statistic (0.738 vs. 0.736, respectively), and ROC curve and therefore we adopted the "full" all-inclusive model for PS scores. The number of matched patients was 4606 for both treatment groups and the standardized difference between dabigatran and warfarin was <0.1 for each tested variable.

**Table 2**
Outcomes in matched cohorts of NVAF patients receiving dabigatran or warfarin.

| Events | Dabigatran (n = 4606) | Warfarin (n = 4606) | HR (95% CI) | p-Value |
|---|---|---|---|---|
| Stroke, systemic embolism, and intracranial bleeding | | | | |
|   Patient-years | 2485 | 3059 | | |
|   Number of events | 72 | 109 | | |
|   Incidence rate (per 1000 patient-years) | 28.98 | 35.63 | 0.72 (0.53–0.97) | 0.0307 |
| Major bleeding | | | | |
|   Patient-years | 2504 | 3103 | | |
|   Number of events | 16 | 35 | | |
|   Incidence rate (per 1000 patient-years) | 6.39 | 11.28 | 0.55 (0.30–0.99) | 0.0478 |
| Major bleeding (intracranial) | | | | |
|   Patient-years | 2518 | 3121 | | |
|   Number of events | 0 | 2 | | |
|   Incidence rate (per 1000 patient-years) | 0 | 0.64 | NA | NA |
| Major bleeding (gastrointestinal) | | | | |
|   Patient-years | 2515 | 3108 | | |
|   Number of events | 4 | 20 | | |
|   Incidence rate (per 1000 patient-years) | 1.59 | 6.43 | 0.24 (0.08–0.69) | 0.0087 |
| Major bleeding (intraocular) | | | | |
|   Patient-years | 2518 | 3121 | | |
|   Number of events | 2 | 1 | | |
|   Incidence rate (per 1000 patient-years) | 0.79 | 0.32 | 2.32 (0.21–25.61) | 0.4929 |
| Major bleeding (other) | | | | |
|   Patient-years | 2508 | 3113 | | |
|   Number of events | 10 | 15 | | |
|   Incidence rate (per 1000 patient-years) | 3.99 | 4.82 | 0.81 (0.36–1.80) | 0.5993 |
| Ischemic stroke, systemic embolism, and TIA | | | | |
|   Patient-years | 2302 | 2821 | | |
|   Number of events | 225 | 305 | | |
|   Incidence rate (per 1000 patient-years) | 97.73 | 108.10 | 0.81 (0.68–0.97) | 0.0178 |
| Intracranial bleeding | | | | |
|   Patient-years | 2502 | 3079 | | |
|   Number of events | 49 | 80 | | |
|   Incidence rate (per 1000 patient-years) | 19.58 | 25.99 | 0.67 (0.47–0.96) | |

HR, hazard ratio; NA, not applicable; NVAF, non-valvular atrial fibrillation; TIA, transient ischemic attack.

*Primary and secondary outcomes in warfarin- and dabigatran-treated patients*

Among patients in the propensity-matched cohorts, the incidence of stroke, systemic embolism, and intracranial bleeding was higher in warfarin recipients than in those who were treated with dabigatran (35.6 vs. 29.0 per 1000 patient-years; HR, 0.72; 95% CI: 0.53–0.97; *p* = 0.031; Table 2). The incidence of major bleeding was higher among patients treated with warfarin compared with those who were treated with dabigatran (11.3 vs. 6.4 per 1000 patient-years; HR, 0.55; 95% CI: 0.30–0.99; *p* = 0.048; Table 2). At 24 months of follow-up, only 601 dabigatran and 467 warfarin recipients remained at risk.

Major gastrointestinal bleedings were more common with warfarin (*n* = 20) than with dabigatran (*n* = 4). The incidence rate of major gastrointestinal bleeding was 6.4 per 1000 patient-years with warfarin and 1.6 per 1000 patient-years with dabigatran (HR, 0.24, 95% CI: 0.08–0.69). The incidences of other types of bleeding are presented in Table 2.

Sensitivity analyses using the Gorst-Rasmussen definition of stroke and SE resulted in a lower incidence of these events in patients treated with dabigatran compared with those who received warfarin (8.0 vs. 14.9 per 1000 patient-years; HR, 0.48; 95% CI: 0.28–0.80; *p* = 0.006; Supplementary Table 3). Using the Gorst-Rasmussen definition of major bleeding also produced a lower incidence of this event in patients who received dabigatran than in those who received warfarin (1.6 vs. 5.8 per 1000 patient-years; HR, 0.27; 95% CI: 0.09–0.80; *p* = 0.018; Supplementary Table 3). Furthermore, a post hoc sensitivity analysis using Kohsaka's definition produced a lower incidence of major bleeding in patients treated with dabigatran than in those who received warfarin (5.2 vs. 16.6 per 1000 patient-years; HR, 0.30; 95% CI: 0.17–0.56; *p* = 0.0001; Supplementary Table 3).

## Discussion

In this retrospective observational study, the MDV database was used to assess the patterns of OAC prescriptions in patients with NVAF and to compare the effectiveness and safety of dabigatran and warfarin. In the present study of patients treated with OACs, approximately one in three Japanese patients with NVAF was initiated on warfarin and approximately one in ten was initiated on dabigatran. These findings are consistent with previous data from registry studies, where warfarin was the most widely prescribed OAC for patients with NVAF in Japan [17–20].

In the present study, dabigatran was associated with a lower risk of stroke, systemic embolism, and intracranial bleeding and a lower risk of major bleeding compared with warfarin in patients with NVAF. Sensitivity analysis using event definitions utilized in other published studies showed consistently lower risk of stroke and SE, as well as of major bleeding, with dabigatran compared with warfarin.

The RELY study showed dabigatran 110 mg to be non-inferior to warfarin, whereas the findings of the present study show a statistically significant reduction in the incidence of stroke in the dabigatran group, with approximately 80% of patients receiving 110 mg dabigatran twice daily. In RELY, 110 mg treatment assignment was randomized, whereas in real world clinical practice, assignment is based on clinician's judgment; the different results in stroke outcome may be due to the different methods utilized in RELY and the present study.

Graham and colleagues evaluated the comparative effectiveness and safety of warfarin and dabigatran in US patients using the Medicare claims database [7]. They found that, compared with warfarin, dabigatran was associated with a reduced risk of ischemic stroke (HR, 0.80; 95% CI: 0.67–0.96) and intracranial hemorrhage (HR, 0.34; 95% CI: 0.26–0.46), but also with an increased risk of major gastrointestinal (GI) hemorrhage (HR, 1.28; 95% CI: 1.14–1.44). In the study by Graham and colleagues, 84% of patients received dabigatran 150 mg twice daily, whereas in the present study, 21% were treated with dabigatran 150 mg twice daily.

The present study findings related to GI bleeding are consistent with the findings from studies that evaluated the risk in lower dose, or 110 mg of dabigatran [8,10]. GI bleeding incidence was reported to be lower in dabigatran 110 mg exposed group compared to warfarin group, with one study reporting a HR = 0.53 in new user cohort [10] and the other study reporting HR of 0.60 [8]. These results are similar to the findings of the present study, for which dabigatran was associated with a lower risk (HR, 0.24; 95% CI: 0.08 to–0.69).

Bengtson and colleagues evaluated the comparative effectiveness of dabigatran and rivaroxaban versus warfarin using data from US MarketScan databases [21]. Like this analysis, they found that, in treatment-naïve patients, dabigatran was associated with lower rates of ischemic stroke (HR, 0.65; 95% CI 0.52–0.82), intracranial bleed (HR, 0.37; 95% CI: 0.20–0.67), and myocardial infarction (HR, 0.72; 95% CI: 0.57–0.91) than warfarin, with no increased risk of GI bleeding. However, these results were not seen in the patients who switched treatment.

Chan and colleagues used the Taiwanese National Health Insurance Research Database and found that, compared with warfarin, dabigatran was associated with a lower risk of ischemic stroke (HR, 0.62; 95% CI: 0.52–0.73), intracranial hemorrhage (HR, 0.44; 95% CI: 0.32–0.60), and bleeding requiring hospitalization (HR, 0.58; 95% CI: 0.46–0.74) [6]. The majority of patients in the Taiwanese study were treated with dabigatran 110 mg twice daily, with only 11% using dabigatran 150 mg twice daily [6]. The findings of Chan and colleagues are consistent with those of the present study.

A retrospective cohort study was conducted in Japan in patients with NVAF initiating treatment with OAC using the same database as the present study [9]. When comparing the two studies, the major difference is that the present study included the risk of stroke and SE as an effectiveness outcome, whereas Kohsaka and colleagues only evaluated bleeding events. The definition of bleeding used by Kohsaka and colleagues was much broader than the one used in the present study. For example, it included claim codes related to trauma, such as traumatic intracranial hemorrhage, and other claim codes that were not included in the definition of major hemorrhage in the present study, such as subcutaneous hemorrhage and positive blood stool. On the other hand, transfusion and hospitalization were used as criteria of major hemorrhage in the current study, while only the latter was used by Kohsaka and colleagues. Despite these differences, Kohsaka and colleagues also observed a lower risk of major bleeding with dabigatran compared with warfarin (HR, 0.617; 95% CI: 0.425–0.895; *p* = 0.011). When Kohsaka and colleagues' definition of major hemorrhage was applied to the data collected in the present study, a much lower risk associated with dabigatran was found (HR, 0.30; 95% CI: 0.17–0.56). It is worth mentioning that the MDV data used in both studies covered an almost identical period.

The findings of the present analysis are also similar to another retrospective study conducted in Japan that compared the effectiveness and safety of dabigatran and warfarin using data from 613 NVAF patients from the Tokyo Women's Medical University Hospital records [8]. Naganuma and colleagues showed that dabigatran had a lower major bleeding rate than warfarin (HR, 0.15; 95% CI: 0.01–0.90; *p* = 0.037). However, unlike our analysis, the risk of thromboembolism was comparable with dabigatran and warfarin (HR, 1.03; 95% CI: 0.12–8.04) [8].

The present study had a number of strengths that primarily concerned the source of data and the rigorous methods of analysis. The analyzed data were derived from a large number of patients in

Japan, comprising both in- and out-patient claims from a sample of the Japanese population. Age and gender distributions of the patients in the database are approximately similar to those of the national patient statistics in Japan [11,22]. The definitions of the primary outcome measures used in the present study were the same as those used by Koretsune and colleagues [13]. These definitions have been shown to have a positive predictive value of 74% for stroke and 87% for SE [13]. Claims-defined diagnoses using DPC data had a specificity of more than 96% [23]. Sensitivity analysis was conducted using definitions utilized by other groups, which showed consistent results. Because real-world clinical data are subject to a variety of biases, PS matching was used to control for confounding, especially channeling bias, which may be attributable to between-group differences in the demographic and clinical characteristics of the patient groups [24].

This study also had several limitations. Firstly, the generalizability of the findings may be limited outside of the population of Asian patients with NVAF. Secondly, the data held in the MDV database are collected from acute care hospitals, not general practice, and may contain out-patient data with greater disease severity than those exclusively seen by small medical clinics. Thirdly, information on each patient was only collected from participating hospitals and did not include any visits that patients made to other medical institutions. This may have caused misclassification of the outcome events resulting in biased estimates and could have contributed to the relatively short duration of follow-up and made the estimates based on survival analysis beyond 24 months less reliable. In addition, variables available in the database may not include important drivers of treatment decisions. Unobservable factors or factors not captured in the database, such as laboratory data, that are not equally distributed in the treatment groups may also influence the outcomes, and could have led to confounding. Furthermore, prothrombin time or international normalized ratio data were not available for analysis, which prevented any interpretation of the level of anticoagulation in the warfarin group.

## Conclusions

In the present study, dabigatran was associated with a lower risk of stroke, SE, and intracranial bleeding, as well as a lower risk of major bleeding, compared with warfarin. These results were in line with those of previously published large-scale studies in Asian patients with AF.

## Author contributions

All authors contributed to the interpretation of the results and provided critical feedback on the manuscript. T.Y. was involved with defining the disease, clinical events and interpreted the obtained results critically. Y.O. designed the study, defined each disease and comorbid conditions by ICD-10 codes, and managed the project. K.I. was involved in preparing the statistical analysis plan. T.H., D.K., and T.S. were involved with the project management and supervision. All authors approved the final manuscript.

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## Conflict of interest

Y.K. has received lecture, advisory, and travel fees from Daiichi Sankyo, Boehringer Ingelheim, Bayer, Bristol-Myers Squibb, and Pfizer. T.Y. has received lecture, advisory, and travel fees from Boehringer Ingelheim, Daiichi Sankyo, Bayer, Pfizer, Bristol-Myers Squibb, Eisai, Mitsubishi Tanabe Pharma, Toa Eiyo, and Ono Pharmaceutical, writing fees from Boehringer Ingelheim, and scholarship funds and non-restricted grants from Boehringer Ingelheim, Daiichi Sankyo, and Mitsubishi Tanabe Pharma. M.Y. has received lecture, advisory, and travel fees from Bristol-Myers Squibb, Boehringer Ingelheim, Bayer, and Daiichi Sankyo, as well as scholarship funds or non-restricted grants from Boehringer Ingelheim. H.U. is a part-time consultant for Eisai Co. and Nippon Boehringer Ingelheim Co., Ltd. and has received a research grant from CAC Croit. Y.O., T.H., K.I., D.K., and T.S. are employees of Nippon Boehringer Ingelheim Co., Ltd.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jjcc.2018.09.004.

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