Effectiveness and safety of dabigatran versus warfarin in “real-world” Japanese patients with atrial fibrillation: A single-center observational study

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ABSTRACT

Background: In “real-world” practice, anticoagulant therapy is indicated for patients whose clinical profiles are not addressed in randomized clinical trials. We assessed the effectiveness and safety of dabigatran versus warfarin in “real-world” Japanese patients with non-valvular atrial fibrillation (NVAF).

Methods: Among 613 NVAF patients who initiated dabigatran or warfarin therapy during the period between 2011 and 2013, 362 patients were included in the study after propensity score adjustment. The median follow-up period was 1.3 years. The effectiveness and safety outcomes were thromboembolism and major bleeding, respectively.

Results: The propensity-matched hazard ratios of thromboembolism and major bleeding with dabigatran were 1.03 (95% CI: 0.12–8.04, p=0.971) and 0.15 (95% CI: 0.01–0.90, p=0.037), respectively.

Conclusions: The ability of dabigatran to prevent thromboembolism is comparable to that of warfarin; however, the major bleeding rate is lower with dabigatran in “real-world” NVAF patients.

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1. Introduction

Atrial fibrillation (AF) is the most common tachyarrhythmia and is a risk factor for stroke [1–4]. Anticoagulant therapy reduces the risk of AF-related stroke [5]. Dabigatran etexilate is an oral direct thrombin inhibitor, which is the first direct-acting oral anticoagulant. The Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) trial demonstrated that 110 mg of dabigatran was associated with rates of stroke/systemic embolism that were similar to the rates observed in patients taking warfarin; moreover, patients taking dabigatran exhibited a lower rate of major hemorrhage compared with that in patients taking warfarin. Dabigatran at a dose of 150 mg was associated with lower rates of stroke/systemic embolism but showed similar rates of major hemorrhage compared with warfarin treatment in non-valvular AF (NVAF) patients at risk of stroke [6]. A sub-analysis of 326 Japanese subjects in the RE-LY trial demonstrated that the efficacy and safety profiles of dabigatran for Japanese AF patients were essentially the same as those for the overall study population [7].

In “real-world” practice, anticoagulant therapy is indicated for patients whose clinical profiles are not addressed in randomized clinical trials. However, few reports have focused on the effectiveness and safety of dabigatran treatment in “real-world” Japanese NVAF patients. The aim of this study is to assess the effectiveness and safety of dabigatran versus warfarin in Japanese NVAF patients who recently initiated drug treatment.

2. Material and methods

2.1. Subjects

We retrospectively analyzed a cohort of 306 consecutive NVAF patients who initiated dabigatran treatment and 307 consecutive NVAF patients who initiated warfarin treatment in the departments of cardiology and neurology, Tokyo Women’s Medical University Hospital, in the period between March 2011 and December 2013. The study protocol was approved by the institutional review board of Tokyo Women’s Medical University Hospital (approval number: 2887-R3, approval date: December 22, 2015).

Follow-up data were obtained at the routine or additional visits to our institution. For patients receiving warfarin, the frequency of prothrombin time-international normalized ratio (PT-INR) testing and follow-up ranged from once per week (if a control value needed to be...
2.2. Outcomes

The effectiveness outcome of the thromboembolic events included fatal or nonfatal ischemic stroke, transient ischemic attack, and other systemic embolism. The safety outcome was major bleeding defined as intracranial hemorrhage observed by imaging, gastrointestinal hemorrhage, or another severe hemorrhage that was fatal or that required endoscopic hemostasis, surgical intervention, hospital admission, or blood transfusion.

2.3. Statistical analysis

The summary data are presented either as the mean ± standard deviation (SD) or as the number of patients. To balance the potential confounders between groups, propensity score matching was applied using the nearest neighbor matching method at a

| Table 1 Baseline characteristics of propensity-matched patients. |
|-----------------------|------------------------|------------------------|------------------------|
| Drug                  | Dabigatran             | Warfarin               | P-Value                |
| Number                | 181                    | 181                    |                        |
| Age, years            | (69–72)                | (69–72)                | 0.650                  |
| Female                | (50%)                  | (51%)                  | 0.907                  |
| Heart failure         | (33%)                  | (33%)                  | 0.483                  |
| Hypertension          | (110[61%])             | (116[64%])             | 0.515                  |
| Diabetes mellitus     | (52[29%])              | (52[29%])              | 0.908                  |
| Previous stroke/TIA   | (53[29%])              | (56[31%])              | 0.731                  |
| Coronary artery disease | (35[19%])            | (32[18%])              | 0.685                  |
| Permanant AF          | (58[32%])              | (57[31%])              | 0.910                  |
| Body weight, kg       | (65[35–104])           | (61[35–125])           | 0.201                  |
| CCl, mL/min           | (72[17–168])           | (68[14–182])           | 0.092                  |
| CHADS2 score          | Mean 1.9 ± 1.5          | 2.0 ± 1.5              | 0.432                  |
|                       | 0                     | 36 (19.9%)             | 24 (13.3%)             |
|                       | 1                     | 48 (26.5%)             | 55 (30.4%)             |
|                       | 2                     | 42 (23.2%)             | 40 (22.1%)             |
|                       | ≥ 4                   | 31 (17.1%)             | 31 (17.1%)             |
| CHA2DS2-VASc score    | Mean 3.0 ± 1.9         | 3.1 ± 1.9              | 0.608                  |
|                       | 0                     | 11 (6.1%)              | 7 (3.9%)               |
|                       | 1                     | 35 (19.3%)             | 34 (18.8%)             |
|                       | 2                     | 28 (15.5%)             | 37 (20.4%)             |
|                       | ≥ 4                   | 37 (20.4%)             | 31 (17.1%)             |
| HAS-BLED score        | Mean 1.5 ± 1.1         | 1.5 ± 1.2              | 0.871                  |
|                       | 0                     | 37 (20.4%)             | 39 (21.6%)             |
|                       | 1                     | 64 (35.4%)             | 58 (32.0%)             |
|                       | 2                     | 47 (26.0%)             | 46 (25.4%)             |
|                       | ≥ 3                   | 33 (18.2%)             | 38 (21.0%)             |
| Concomitant medications | Aspirin               | 34 (19%)               | 35 (19%)               | 0.894 |
|                       | Other anti-platelet    | 17 (9%)                | 15 (8%)                | 0.711 |
|                       | ACE inhibitor/ARB      | 95 (52%)               | 91 (50%)               | 0.674 |
|                       | Beta-blocker           | 82 (45%)               | 92 (51%)               | 0.293 |
| Calcium channel blocker | 64 (35%)              | 62 (34%)               | 0.825                  |
| Digoxin               | 30 (17%)               | 31 (17%)               | 0.888                  |
| Statin                | 52 (29%)               | 53 (29%)               | 0.908                  |
| Antiarrhythmic drugs  | 45 (25%)               | 45 (25%)               | 0.455                  |

The values are expressed as n (%), mean ± SD, or median (range).

ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; CrCl, creatinine clearance; TIA, transient ischemic attack; CHADS2 = cardiac failure, hypertension, age ≥ 75 years, diabetes, previous stroke or TIA (doubled).



Fig. 1. Kaplan–Meier curves were plotted for the cumulative hazard of thromboembolism in propensity-matched dabigatran and warfarin patients with non-valvular atrial fibrillation.

Fig. 2. Kaplan–Meier curves were plotted for the cumulative hazard of major bleeding in propensity-matched dabigatran and warfarin patients with non-valvular atrial fibrillation.
fixed ratio of 1:1. A multivariable logistic regression model, using the baseline variables as covariates, was used to estimate the propensity for each patient, which predicts the probability of receiving dabigatran versus warfarin treatment given prespecified baseline variables. The baseline clinical data were compared between the groups using Student’s t-test and Wilcoxon rank sum test. Categorical variables were compared using Chi-square analysis. The effectiveness and safety outcome analyses were performed using Cox proportional hazards model. Kaplan–Meier curves were plotted to analyze the cumulative hazard of thromboembolism and major bleeding in the propensity-matched dabigatran and warfarin patients. Time in the therapeutic range (TTR), i.e., the percentage of time during which the PT-INR was within the therapeutic range (1.60–2.59) based on the target PT-INR for low intensity in Japanese clinical practice, was calculated using the Rosendaal linear interpolation method [8]. P-values < 0.05 were considered statistically significant. The data analyses were performed using JMP11 statistical software (version 11.2, SAS Institute, Cary, NC, USA).

3. Results

3.1. Characteristics of the patients

Following propensity score matching with a 1:1 ratio, 362 patients were included in the cohort, including 181 patients in the dabigatran group and 181 patients in the warfarin group. The baseline characteristics of the propensity-matched patients are outlined in Table 1. The median follow-up period was 13 years with a range of 0.1–4.7 years. The total person-times of observation were 315 person-years and 312 person-years in the dabigatran and warfarin groups, respectively. In the dabigatran group, 8 patients received 75 mg twice daily, 124 patients received 110 mg twice daily and 49 patients received 150 mg twice daily. Thirty-six (20%) patients received a lower dosage; however, the reasons for choosing the dosage were heterogeneous and were based on the physician’s decisions: age > 80 years, history of warfarin-induced hepatotoxicity, frequent bleeding episodes, and activated partial thromboplastin time (APTT) prolongation > 80 s. The mean TTR during both the initiation (starting dose and titration to reach the therapeutic range of PT-INR) and maintenance phases of warfarin therapy was 60 ± 27%.

4. Discussion

Our propensity-matched cohort study of “real-world” NVAF patients who initiated treatment with dabigatran or warfarin showed that the incidence of stroke/systemic embolism in patients taking dabigatran was similar to that in patients taking warfarin, whereas the incidence of major bleeding was lower in the dabigatran group. In our propensity-matched patients, the proportion of females (28%), the proportion of heart failure (17%), the proportion of hypertension (62%), the mean CHADS₂ score (1.9), and the proportion of CHADS₂ ≥ 2 (55%) were lower compared with those in the RE-LY trial overall/Japanese (37%/23%, 32%/31%, 79%/-, 2.1/2.2, and 66%/69%, respectively) [6,7]. These differences suggest that our patients have a slightly lower cerebrovascular risk. The majority of our patients received a dabigatran dose of 110 mg, and the current results are comparable to those observed in patients taking the 110-mg dose of dabigatran in the RE-LY trial [6].

A meta-analysis of seven observational studies, comparing dabigatran with warfarin, indicated that the ability of dabigatran to prevent ischemic stroke and bleeding outcomes is comparable to that of warfarin, which is consistent with the data obtained from the RE-LY trial [9]. These findings do not differ between the Japanese patients and the U.S. and European cohorts.

In the present study, the mean CHADS₂ score (1.9) was higher than the scores of the patients who received 150 mg of dabigatran (1.0) and those who received 110 mg of dabigatran (1.3) observed...
in a Danish cohort [10], and the mean CHA2DS2-VASc score (3.0) was lower than the score of the Taiwanese cohort (4.2, patients primarily received 110 mg of dabigatran) [11]. The rates of thromboembolism and major bleeding in this study were lower than those described in previous cohorts [10–12]. Differences between national population-based and hospital-based cohorts may partially contribute to these results.

Two limitations of our study were that this was a retrospective cohort study at a single center and that the sample size was small. Sub-group analysis was not feasible.

5. Conclusions

In conclusion, our propensity-matched analysis demonstrated that the ability of dabigatran to prevent thromboembolism is comparable to that of warfarin; however, the incidence of major bleeding is lower with dabigatran treatment in “real-world” NVAF patients.

Conflict of interest disclosures

Dr. Shiga received lecture fees from Eisai and Nippon Boehringer Ingelheim. Dr. Nagao received lecture fees from Nippon Boehringer Ingelheim. Dr. Hagiwara received research funding and lecture fees from Nippon Boehringer Ingelheim. Ms. Naganuma, Dr. Murasaki and Dr. Suzuki have no conflict of interest to disclose.

Competing interests

The authors have no competing interests to declare.

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