Examination of Time-to-onset of Interstitial Lung Disease, Cerebral Hemorrhage, and Gastrointestinal Hemorrhage in Very Elderly Patients with Atrial Fibrillation Treated with Direct Oral Anticoagulant Using Data from the Japanese Adverse Drug Event Report (JADER) Database

Kimihiko TANIZAWA¹,², *, Hirofumi SUZUKI¹, Hiroaki YAMADA³, Satoshi TOYOSHIMA⁴, and Naomi NAGAI¹

Abstract

We examined the time-to-onset of interstitial lung disease, cerebral hemorrhage, and gastrointestinal hemorrhage in very elderly patients with atrial fibrillation treated with direct oral anticoagulants (DOACs) by using data from the Japanese Adverse Drug Event Report Database (JADER). We compared the time-to-onset of each adverse drug reaction (ADR) based on age or dose for each DOACs. The median values of the time-to-onset ranged from 40 to 124 days for interstitial lung disease while those for gastrointestinal hemorrhage ranged from 60.5 to 91 days, they were no significant difference between the age or drug-dose groups. For cerebral hemorrhage, the median values ranged from 124.5 to 331.5 days, therefore the time-to-onset of cerebral hemorrhage was delayed compared to that of gastrointestinal hemorrhage. Especially, the median value of the factor Xa inhibitors (FXA) high dose (HD) and age 80≤ group showed 331.5 days, which was delayed compared to that in the FXA low dose (LD) and age 80≤ group’s 143 days or the FXA HD and age <80 group’s 175 days. The cerebral hemorrhage occurred not less than a year after dosing, and therefore symptoms of cerebral hemorrhage and continuous symptom management of hypertension need to be carefully monitored in not only early stage but also late treatment stages in FXA HD and age 80≤ patients. This study showed that the analysis using JEDAR could enhance understanding of the time-to-onset of ADRs in very elderly, which were difficult to be collected in clinical trials during drug development. Furthermore, it was suggested that time-to-onset of each ADRs was independently occurred. These findings contribute to grasp time-to-onset of the ADRs and appropriate management of ADRs in the clinical practice.

¹ Laboratory of Regulatory Science, Graduate School of Pharmaceutical Sciences, Musashino University (1-1-20 Sinmachi, Nishitokyo-shi, Tokyo 202-8585, Japan)
² Daiichi Sankyo Co., Ltd.
³ Laboratory of Regulatory Science, Yokohama University of Pharmacy
⁴ Japan Pharmacists Education Center
* Corresponding author
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Introduction

It has been reported that Japan’s aging population will continue to increase significantly, and the proportion of people aged more than 75 years to the total population was 5% in 1990, 13% in 2015, and will reach 27% in 2060\(^1\). The elderly tend to contract various heart diseases such as atrial fibrillation (AF), which is a common type of arrhythmia in the elderly. Furthermore, it is well known that the prevalence of AF increases with age\(^2\). Oral anticoagulant therapy is recommended as the standard pharmacotherapy for the prevention of stroke in patients with AF in Japan and internationally\(^3-4\). In Japan, until 2010, the vitamin K antagonist, warfarin, was the only available oral anticoagulant that could be used in patients with AF. The direct thrombin inhibitor (DTI), dabigatran etexilate methanesulfonate (dabigatran) was on the market in 2011, followed by the introduction of the factor Xa inhibitors (FXAs) rivaroxaban in 2012, apixaban in 2013, and edoxaban tosilate hydrate (edoxaban) in 2014\(^5-8\). These direct oral anticoagulants (DOACs) have less interactive effects, and therefore, regular coagulation tests is not required, unlike warfarin. DOAC treatment has prevailed in not only young but also in very elderly patients with AF. However, data or information in very elderly patients are limited because the mean age of patients in the clinical trials is 5-10 years lower than the average age of patients with AF in the general population, even though most AF trials have enrolled patients without an upper age limit\(^9\). Few research studies have reported on this age group including on the time-to-onset of ADRs.

The Japanese Adverse Drug Event Report (JADER) reflects the realities of clinical practice, and is available on the Pharmaceuticals and Medical Devices Agency (PMDA) website.

The objective of the present study was to examine the time-to-onset of ADRs in very elderly patients with AF treated with DOACs in Japan.

Methods

Data sources: ADRs data from the JADER
database downloaded from the PMDA website on May 1st, 2017. The analysis datasets were prepared using Microsoft Access 2010 (Microsoft Inc.).

Drugs: Dabigatran (a DTI), and rivaroxaban, apixaban, and edoxaban (FXAs) approved in Japan. The first administered dose was used for analysis in this study in Table 1.

The adverse drug reaction (ADR): We selected interstitial lung disease, cerebral and gastrointestinal hemorrhage. Bleeding of DOACs has been recognized as a common adverse reaction, especially cerebral hemorrhage or gastrointestinal hemorrhage was severe adverse reaction that would cause death or fatal. Interstitial lung was also severe adverse reaction, and was able to be compared another report which already caused by gefitinib or imatinib or a herbal medicinal product (shosaikoto). These ADRs are listed as important identified risks or important potential risks in the risk management plan. The ADR determination relied on definitions provided by the MedDRA version 20.0. We used the Standardized MedDRA Query (SMQ) for interstitial lung disease (SMQ code: 20000042). The number of selected preferred terms for interstitial lung disease was 62. We used 61 preferred terms each that matched the SMQ for cerebral and gastrointestinal hemorrhage (SMQ codes: 20000108 and 20000064, respectively).

Outcome: The percentage fatal outcomes except for the unknown outcome were calculated in each drug-dose and age group.

Data on the time-to-onset dates: The data that missed the beginning date of dosing or the occurrence date of ADRs was excluded. The date recorded had only the year and month was designated the day as the 1st. The occurrence date of the first ADR was used if multiplicate ADRs occurred.

Data on age: The missing data, unknown, or the unclearly data were excluded. The data on age in the JADER were divided by 10 years. To evaluate the effect of age on ADRs, the reports were stratified into two age groups: <80 and 80≤ years old (<80 and 80≤, respectively).

The complete reports with date, dosage and age were analyzed. The Mann-Whitney U tests were performed using EZR. The box plot and the Weibull distribution were performed using the JMP 13.0 program (SAS Institute Inc., USA).

<table>
<thead>
<tr>
<th>Drug-Dose group</th>
<th>Drug</th>
<th>Dosage and administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>FXA LD</td>
<td>rivaroxaban</td>
<td>10 mg QD</td>
</tr>
<tr>
<td></td>
<td>apixaban</td>
<td>2.5 mg BID</td>
</tr>
<tr>
<td></td>
<td>edoxaban</td>
<td>30 mg QD</td>
</tr>
<tr>
<td>FXA HD</td>
<td>rivaroxaban</td>
<td>15 mg QD</td>
</tr>
<tr>
<td></td>
<td>apixaban</td>
<td>5 mg BID</td>
</tr>
<tr>
<td></td>
<td>edoxaban</td>
<td>60 mg QD</td>
</tr>
<tr>
<td>DTI LD</td>
<td>dabigatran</td>
<td>110 mg BID</td>
</tr>
<tr>
<td>DTI HD</td>
<td>dabigatran</td>
<td>150 mg BID</td>
</tr>
</tbody>
</table>

FXA, factor Xa inhibitor; DTI, direct thrombin inhibitor; HD, high dose; LD, low dose; QD, quaque die; BID, bis in die
Results

The number of reports in the JADER database was 445,706 reports and combinations of drugs and ADRs was 691,071 cases. The ADRs where DOACs were the suspected drug for patients with AF were 8272 cases. Furthermore, the number of ADRs of interstitial lung disease, cerebral hemorrhage, and gastrointestinal hemorrhage were 357, 1659, and 1494 cases respectively. In addition, the corresponding number of cases missing the beginning date of dosing were 56, 466, and 273 cases respectively and those missing the occurrence date of the ADRs or age were 35, 91, and 107 cases, respectively. As a result, the cases included in the analysis of interstitial lung disease, cerebral hemorrhage, and gastrointestinal hemorrhage were 266 (74.5%: 266/357), 1102 (66.4%: 1102/1659), and 1114 cases (74.6%: 1114/1494), respectively. The number of each ADR in the DTI HD and age 80≤ group was less compared to that of the other drug-dose and age groups (Fig. 1).

Table 2 shows the percentage fatal outcome in each group, which differed for each ADR. For interstitial lung disease, no difference occurred in the dose group of each drug while the percentage fatal outcome was nearly 20 in the <80

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**Fig. 1** Flow diagram of statistical analysis.

FXA, factor Xa inhibitor; DTI, direct thrombin inhibitor; HD, high dose; LD, low dose.
group and 30–40% in 80 ≤ group, respectively. For cerebral hemorrhage, the percentage fatal outcome was 10% to 30% while for gastrointestinal hemorrhage, the value was 2.3% to 20%, which was less than that of cerebral hemorrhage. The percentage fatal outcome in gastrointestinal hemorrhage for DTI groups tended to show higher values than that for the FXA groups.

1. Interstitial lung disease

The box plot and histogram of the time-to-onset of interstitial lung disease are shown in Fig. 2. The median values (interquartile range) were from 40 (14–194) days in the DTI LD and age 80 years old ≤ group to 124 (25.5–201.5) days in the FXA LD and age <80 group. The minimum and maximum were 0 and 1258 days, respectively. There was no significant difference in the time-to-onset for the age or drug-dose group. The Weibull scale and shape parameters of interstitial lung disease were summarized in Table 3. The upper 95%CI of β in the FXA LD and age <80 group slightly exceeded 1, but that in other groups did not. This finding suggests that the time profile was the early failures type.

2. Cerebral hemorrhage

The box plot and histogram of the time-to-onset of cerebral hemorrhage are shown in Fig. 3. The median values (interquartile range) were from 124.5 (28.25–296.75) days in DTI LD and age 80 ≤ group to 331.5 (160–545.5) days in the FXA HD and age 80 ≤ group. The occurrence date of cerebral hemorrhage in the FXA HD and age 80 ≤ group was delayed compared to those in the FXA LD and age 80 ≤ and FXA HD and age <80 groups (P = 0.00052 and P = 0.0052, respectively). The minimum and maximum were 0 and 1984 days, respectively. The Weibull scale and shape parameters of cerebral hemorrhage were summarized in Table 4. The upper 95%CI of β, except for the FXA HD and age 80 ≤ group and FXA LD and age <80 group, did not exceed 1. This result indicates that the time profile was the early failures type. Furthermore, the Weibull β shape parameter of the FXA HD and age 80 ≤ group was 1.209 and the lower 95%CI of β dropped slightly below 1. The β parameter was estimated at almost 1, which classified it as a random failures type.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Drug Dose</th>
<th>interstitial lung disease</th>
<th>cerebral hemorrhage</th>
<th>gastrointestinal hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;80</td>
<td>FXA LD</td>
<td>18.9% (7/37)</td>
<td>23.8% (45/189)</td>
<td>38% (5/131)</td>
</tr>
<tr>
<td></td>
<td>FXA HD</td>
<td>16.9% (11/65)</td>
<td>21.2% (72/340)</td>
<td>27% (7/264)</td>
</tr>
<tr>
<td>80 ≤</td>
<td>FXA LD</td>
<td>35.4% (23/65)</td>
<td>23.7% (61/257)</td>
<td>8.6% (27/313)</td>
</tr>
<tr>
<td></td>
<td>FXA HD</td>
<td>31.3% (5/16)</td>
<td>17.0% (8/47)</td>
<td>23% (1/43)</td>
</tr>
<tr>
<td>&lt;80</td>
<td>DTI LD</td>
<td>18.2% (6/33)</td>
<td>9.7% (7/72)</td>
<td>4.4% (5/113)</td>
</tr>
<tr>
<td></td>
<td>DTI HD</td>
<td>16.7% (2/12)</td>
<td>27.8% (5/18)</td>
<td>6.1% (2/33)</td>
</tr>
<tr>
<td>80 ≤</td>
<td>DTI LD</td>
<td>40.0% (10/25)</td>
<td>15.9% (11/69)</td>
<td>13.7% (19/139)</td>
</tr>
<tr>
<td></td>
<td>DTI HD</td>
<td>0.0% (0/2)</td>
<td>0.0% (0/3)</td>
<td>20.0% (2/10)</td>
</tr>
</tbody>
</table>

FXA, factor Xa inhibitor; DTI, direct thrombin inhibitor; HD, high dose; LD, low dose.
3. Gastrointestinal hemorrhage

The box plot and histogram of the time-to-onset of gastrointestinal hemorrhage are shown in Fig. 4. The median values (interquartile range) were from 60.5 (20.25–182) days in the FXA LD and age 80≤ group to 91 (19–279) days in the FXA HD and age <80 group. The minimum and maximum were 0 and 2015 days, respectively. There was no significant difference in the time-to-onset for the age or drug-dose

Table 3  Weibull scale and shape parameters of interstitial lung disease

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Drug Dose</th>
<th>number</th>
<th>Scale parameter: $a$ (95%CI)</th>
<th>Shape parameter: $\beta$ (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;80</td>
<td>FXA LD</td>
<td>39</td>
<td>152.9 (99.1–231.3)</td>
<td>0.802 (0.614–1.017)</td>
</tr>
<tr>
<td></td>
<td>FXA HD</td>
<td>66</td>
<td>189.6 (137.8–257.7)</td>
<td>0.827 (0.681–0.988)</td>
</tr>
<tr>
<td>80≤</td>
<td>FXA LD</td>
<td>69</td>
<td>156 (110.7–217)</td>
<td>0.752 (0.619–0.898)</td>
</tr>
<tr>
<td></td>
<td>FXA HD</td>
<td>16</td>
<td>83.5 (38–175.8)</td>
<td>0.717 (0.482–0.988)</td>
</tr>
<tr>
<td>&lt;80</td>
<td>DTI LD</td>
<td>36</td>
<td>140.5 (83–232.1)</td>
<td>0.7 (0.532–0.889)</td>
</tr>
<tr>
<td></td>
<td>DTI HD</td>
<td>13</td>
<td>166.3 (49.8–512.2)</td>
<td>0.589 (0.352–0.893)</td>
</tr>
<tr>
<td>80≤</td>
<td>DTI LD</td>
<td>25</td>
<td>129.3 (64.9–248)</td>
<td>0.658 (0.471–0.877)</td>
</tr>
<tr>
<td></td>
<td>DTI HD</td>
<td>2</td>
<td>238 (3.9–158.1)</td>
<td>1.465 (0.321–3.955)</td>
</tr>
</tbody>
</table>

CI, confidence interval, FXA, factor Xa inhibitor; DTI, direct thrombin inhibitor; HD, high dose; LD, low dose.
groups. The Weibull scale and shape parameters of gastrointestinal hemorrhage were summarized in Table 5. The upper 95% CI of $\beta$ did not exceed 1, which suggests that the time profile was the early failures type.

Table 6 shows the list of patients who experienced cerebral and gastrointestinal hemorrhage in 17 patients in this study. Nine and five
patients first exhibited cerebral and gastrointestinal hemorrhage, respectively while three cases exhibited these symptoms on the same day.

**Discussion**

In this study, we examined the time-to-onset of each ADR in very elderly patients with AF treated with the DOAC using data from the
JADER database. The number of ADRs in patients 80 ≤ years old in the FXA LD group was 284 cases for cerebral hemorrhage and 330 cases for gastrointestinal hemorrhage, respectively. Therefore, the JADER data subset is useful for analysis of time-to-onset of ADRs, which were difficult to be collected in clinical trials, in very elderly patients under certain limited conditions.

DOACs reduce the incidence of cerebral hemorrhage compared with warfarin, especially in East Asia\(^{16-20}\). In this study, there were 1102 cases of cerebral hemorrhage, and we determined the time-to-onset of the cerebral hemorrhage. A quarter of the cerebral hemorrhage cases occurred within 2 months after the beginning of dosing, but the median values were from 124.5 to 175 days (3 to 5 months), except for the FXA HD and age 80 ≤ group in Fig. 3. The median value was 331.5 days in the FXA HD and age 80 ≤ group, which was delayed, compared to 175 days for the FXA LD and age 80 ≤ years old and 143 days for FXA HD and age < 80 groups, respectively. Furthermore, the Weibull \(\beta\) shape parameter of the FXA HD and age 80 ≤ group was 1.209, and therefore, it was classified as a random failures type. There were different patient characteristics in the FXA HD and age 80 ≤ group and further scrutiny of data is needed to understand the implications of the time-to-onset of cerebral hemorrhage.

It is well known that risk factors of cerebral hemorrhage include hypertension, diabetes, heart disease and arrhythmias, hyperlipidemia, and smoking, particularly hypertension is the greatest risk factor\(^{21}\). Patients with hypertension, require continuous symptom management and patient education on the nature of their condition. The patients who was treated FXA HD and age 80 ≤ year old also need to be carefully monitored symptoms in both the early and the late treatment stages.

The median values (interquartile range) of interstitial lung disease incidences were reported as 28 (13–64) days for gefitinib, 135 (67–304) days for imatinib, and 37 (15–80) days for a
herbal medicinal product (shosaikoto), while the Weibull $\beta$ shape parameter (95%CI) was 0.84 (0.80–0.88), 1.32 (1.14–1.51), and 0.83 (0.64–1.04), respectively$^{11}$. In this study, the median values (interquartile range) were from 40 (14–194) days in the DTI LD and age <80 group to 124 (25.5–201.5) days in the FXA LD and age <80 group. The Weibull $\beta$ shape parameter was <1, although the 95%CI showed a wide range because of the small number of ADRs in each drug-dose group. The interstitial lung disease cases induced by the FXAs or DTIs were classified as the early failures type similar to that caused by gefitinib. The treatment guideline for disorders due to ADRs focusing on interstitial lung disease was published in November 2016$^{22}$. Early detection of interstitial lung disease is critical because the condition is potentially lethal. In this study, the fatal outcome was nearly 20 and 30% in the <80 and 80≤ groups, respectively. It is recommended to monitor patients for the first symptoms of interstitial lung disease, which may occur.

The median value (interquartile range) of gastrointestinal hemorrhage incidences was shorter than that of cerebral hemorrhage. Gastrointestinal hemorrhage is a risk factor for major bleeding, and the fatal outcome in gastrointestinal hemorrhage in the 80≤ groups was approximately two-fold greater than that in <80 groups. The meta-analysis of gastrointestinal hemorrhage in patients treated with DOAC reported that DOAC had the same risk as that of vitamin K antagonists (relative risk [RR]: 1.08, 95%CI: 0.85–1.36)$^{23}$. The retrospective cohort study revealed that the gastrointestinal hemorrhage risk was higher in 75< years old patients (RR: 2.47, 95%CI: 1.66–3.68), with a history of peptic ulcer or gastrointestinal hemorrhage (RR: 2.31, 95%CI: 1.54–3.46), or who were coadministered aspirin (RR: 1.52, 95%CI: 1.03–2.24)$^{24}$. This cohort study also indicated that coadministration of a proton pump inhibitor or histamine H2-receptor antagonist reduces the risk of gastrointestinal hemorrhage (RR: 0.52, 95%CI: 0.35–0.77). It is important to monitor symptoms of gastrointestinal hemorrhage, in consideration of underlying diseases and concomitant use of other drugs such as antiplatelet drugs or proton pump inhibitors.

Gastrointestinal hemorrhage complicated the condition of 3% of patients who had cerebral hemorrhage, and there are reports of more severe effects in older patients and those with serious conditions$^{25}$. Nine and five patients first had cerebral and gastrointestinal hemorrhage, respectively while three cases had experiences on the same day in this study. The relationship between cerebral and gastrointestinal hemorrhage was not clear, but such ADRs occurred within 1 month in 10 patients, half of whom were in the 80≤ groups.

There are some limitations in the analysis of data from the JADER database. As generally mentioned, there are subject to various biases, including under-reporting, missing data for the initial dosing date, the occurrence date of ADRs, and age. The number of reported ADRs increases with increasing sales amount or number of patients administered the drugs$^{26–27}$. We do not know the number of patients administered each DOAC and could not calculate the incidence rate of each ADR. Although it is important to cautiously interpret the results of this study, it could be emphasized that the cerebral hemorrhage occurred not less than a year after dosing, and therefore, symptoms of cerebral hemorrhage and continuous symptom management of
hypertension need to be carefully monitored in not only early stage but also late treatment stages in FXA high dose treated and age 80≤ patients.

**Conclusion**

We examined the time-to-onset of interstitial lung disease, cerebral hemorrhage, and gastrointestinal hemorrhage in very elderly patients with AF who were treated with DOACs using data from the JADER database. The comparison of the time-to-onset of each ADRs based on age and dose for each DOAC, showed no significant differences for interstitial lung disease and gastrointestinal hemorrhage. The occurrence date of cerebral hemorrhage was delayed compared to gastrointestinal hemorrhage. Furthermore, the occurrence date of cerebral hemorrhage in the FXA HD and age 80≤ group was delayed compared to that in the FXA LD and age 80≤ and FXA HD and age <80 groups. Therefore, symptoms of cerebral hemorrhage and continuous symptom management of hypertension need to be carefully monitored in not only early stage but also late treatment stages in FXA high dose treated and age 80≤ patients.

This study showed that the analysis using JEDAR could enhance understanding of the time-to-onset of ADRs in very elderly, which were difficult to be collected in clinical trials during drug development. Furthermore, it was suggested that time-to-onset of each ADR was independently occurred. These findings contribute to grasp time-to-onset of ADRs and appropriate management of ADRs in the clinical practice.

**Conflict of interest**

K. T. is an employee of Daiichi Sankyo. H. S., H. Y., S. T., and N. N. have no conflict of interest to declare.

**References**


12) RMP: Risk Management Plan


Note

*1 The Weibull distribution has standard and shape parameters (α and β, respectively). The shape
parameter $\beta$ is known to be indicative of changes in the hazard over time. When parameter $\beta$ was estimated at almost 1, it was considered as a random failure type. If the upper 95% confidence interval (CI) was $<1$, the time profile was considered an early failure type. Alternatively, when the lower 95% CI was $<1$, the time profile was the wear-out failure type.