Trends in Prevalence of Non-Valvular Atrial Fibrillation and Anticoagulation Therapy in a Japanese Region
— Analysis Using the National Health Insurance Database —

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Background: Direct oral anticoagulants (DOACs) are effective in reducing thromboembolism events in patients with non-valvular atrial fibrillation (NVAF). However, little is known about trends in NVAF prevalence and DOAC prescriptions in daily clinical practice. This study investigated the current status and trends in NVAF prevalence and DOAC prescriptions in a region of Japan.

Methods and Results: Annual data for the 4 years from May 2014 to May 2017 in the Tsugaru region of Aomori Prefecture, Japan, were obtained for analysis from the Japanese National Health Insurance database ("Kokuho" database [KDB]). The prevalence of NVAF in subjects aged 40–74 years increased gradually over the 4-year study period (1,094/57,452 [1.90%] in 2014, 1,055/56,018 [1.88%] in 2015, 1,072/54,256 [1.98%] in 2016, and 1,154/52,341 [2.20%] in 2017). The proportion of NVAF patients prescribed warfarin decreased (42%, 33%, 24%, and 21% in 2014, 2015, 2016, and 2017, respectively), the proportion of those prescribed DOACs increased (30%, 42%, 50%, and 57%, respectively), and the proportion not prescribed an oral anticoagulant (OAC) decreased (28%, 25%, 26%, and 22%, respectively). However, 17% of patients with a CHADS2 score ≥2 were not prescribed an OAC in 2017.

Conclusions: By using the KDB we found that the prevalence of NVAF has increased gradually from 2014 to 2017. In the Tsugaru region in Japan, DOACs prescriptions increased and warfarin prescriptions decreased over the 4-year period.

Key Words: Direct oral anticoagulant; Kokuho database; Warfarin

Atrial fibrillation (AF) is a common arrhythmia in elderly people and is a common cause of cardioembolic stroke. According to the results of a 2006 Japanese community-based study, AF is observed in 0.5% of men and 0.2% of women aged 40–59 years, in 2.3% of men and 1.0% of women aged 60–79 years, and in 3.5% of men and 2.5% of women aged ≥80 years.1 A similar prevalence of AF was reported using the data from Japanese periodic health examinations in 2003.2 In Korean general health screening tests, the prevalence of AF was 1.2% in men and 0.4% in women aged ≥40 years, and 3.3% in men and 1.1% in women aged ≥65 years,3 which is similar to the prevalence of AF in the Japanese population. In contrast, the prevalence of AF in the US population was 0.9% in men and 0.4% in women aged 55–59 years, increasing to >10% in men and >7% in women aged ≥80 years.4 Consistent with these findings, a recent review found that Australia, Europe, and the US have the highest reported prevalence of AF.5 These findings indicate a lower prevalence of AF in Asian populations. However, limited data are available regarding recent AF prevalence and its trend in the Japanese population.

For many decades, warfarin was the only oral anticoagulant (OAC) that reduced the risk of cardioembolic stroke in patients with AF; however, from 2011, direct OACs (DOACs) became available in Japan. Several large randomized controlled trials have shown that DOACs produce...
Table 1. Patient’s Characteristics in Each Year of the Study

|                      | 2014 (n=1,094) | 2015 (n=1,055) | 2016 (n=1,072) | 2017 (n=1,154) | P-value 
|----------------------|----------------|----------------|----------------|----------------|--------
| NVAF prevalence (%)  | 1.90 (1,094/57,452) | 1.88 (1,055/56,018) | 1.98 (1,072/54,256) | 2.20 (1,154/52,341) |
| Age-adjusted NVAF prevalence (%) | 1.90 (Ref.) | 1.84 | 1.91 | 2.09 |
| Age group (years)    |                |                |                |                | <0.001
| 40–64                | 306 (28)       | 243 (23)       | 195 (18)       | 243 (21)       |
| 65–74                | 788 (72)       | 812 (77)       | 877 (82)       | 911 (79)       |
| Men                  | 738 (67)       | 725 (69)       | 742 (69)       | 807 (70)       |
| Mean (±SD) CHADS2 score | 2.15±1.31     | 2.20±1.30      | 2.12±1.31      | 2.12±1.25      |
| CHADS2 scores        |                |                |                |                | 0.75   |
| 0                    | 90 (8)         | 76 (7)         | 96 (9)         | 85 (7)         |
| 1                    | 296 (27)       | 277 (26)       | 288 (27)       | 311 (27)       |
| ≥2                   | 708 (65)       | 702 (67)       | 688 (64)       | 758 (66)       |
| Comorbidities        |                |                |                |                |        |
| Heart failure        | 563 (51)       | 542 (51)       | 546 (51)       | 594 (51)       |
| Hypertension         | 861 (79)       | 835 (79)       | 833 (78)       | 911 (79)       |
| Diabetes             | 423 (39)       | 435 (41)       | 414 (39)       | 463 (40)       |
| Stroke and TIA       | 253 (23)       | 252 (24)       | 238 (22)       | 240 (21)       |

Unless indicated otherwise, data are presented as n (%). The age-adjusted prevalence of non-valvular atrial fibrillation (NVAF) in each year was calculated using the age distribution in 2014 as a reference. TIA, transient ischemic attack.

equal or significantly greater reductions in the risk of stroke or systemic embolism, as well as major bleeding, in non-valvular AF (NVAF) patients compared with warfarin. Therefore, guidelines for the treatment of NVAF have recommended DOACs as first-line therapy for eligible patients. Observational and registry studies in Denmark, Canada, and Japan have shown year-on-year increases in the prescription of DOACs. However, little is known about trends in DOAC prescriptions in daily clinical practice.

The Japanese National Health Insurance database (the “Kokuho” database [KDB]) provides comprehensive patient information regarding diagnoses, diagnostic codes, and prescriptions, and is available as a resource for various analyses. Information on comorbidities for individual patients and OACs prescribed by physicians in a region can be obtained from this database. In the present study we investigated the current status and trends in NVAF prevalence and OAC prescription in the Tsugaru region in Japan using the KDB. We believe that the present study is the first to systematically investigate trends in NVAF prevalence and OAC prescription for Japanese NVAF patients using the KDB.

Methods

Study Design and NVAF Prevalence

The study protocol was approved by the Ethics Committee of the Hirosaki University Graduate School of Medicine (2016-095). The present study was a retrospective cross-sectional study based on data already registered in the KDB; therefore, the requirement for obtaining written informed consent from each patient was waived. However, an opt-out policy was implemented, allowing patients to refuse the use of their data for this study.

Subjects aged 574 years were registered in the KDB, and data from those aged 40–74 years were used in the present study. The number of patients with AF, hypertension, heart failure, diabetes, and a history of previous stroke/transient ischemic attack (TIA) was evaluated using the name of the diagnosis in the Kokuho claim. Patient data, including diagnosis and medication, were collected from the KDB once a year (May) for the present study by public health nurses and registered dietitians in 2014, 2015, 2016, and 2017 in the Tsugaru region of Aomori Prefecture, located in the northern part of the Japanese main island. This region includes Hirosaki City, Hirakawa City, Fujisaki Town, Itayanagi Town, and Inakadate Village. Over the 4-year study period, the total population in this region aged 40–74 years decreased gradually from 121,139 in 2014, 120,745 in 2015, 119,967 in 2016, to 119,069 in 2017. The KDB coverage rate during the period between 2014 and 2017 was calculated and was shown to increase gradually with increasing age (23% for those aged 40–44 years, 26% for those aged 45–49 years, 30% for those aged 50–54 years, 36% for those aged 55–59 years, 55% for those aged 60–64 years, 69% for those aged 65–69 years, and 76% for those aged 70–74 years; Supplementary Table). Importantly, total subscribers decreased from 57,452 in 2014 to 52,335 in 2017, due primarily to a decrease in relatively younger subscribers (aged 40–44 years) over the 4 years. Conversely, the number of older subscribers (aged 65–74 years) was similar or increased from 2014 to 2017. After exclusion of valvular AF (n=14 in 2014, n=9 in 2015, n=12 in 2016, and n=10 in 2017) and 6 NVAF patients who refused to allow their data to be used, the number of NVAF patients included in the present study was 1,094 in 2014, 1,055 in 2015, 1,072 in 2016, and 1,154 in 2017.

Data were collected for the prevalence of NVAF in each 5-year age group for men and women living in the Tsugaru region. An indirect age standardization for the comparison of NVAF prevalence in each year from 2014 to 2017 was performed using the age distribution in 2014 as a reference. The prevalence of NVAF and comorbidities in the present study were compared with those in various Japanese studies, including the report of Ohsawa et al using data from a
Results

Prevalence of NVAF

The estimated prevalence of NVAF in the Tsugaru region increased gradually over the 4 years (1.90% in 2014, 1.88% in 2015, 1.98% in 2016, and 2.20% in 2017; Table 1). However, age-adjusted NVAF prevalence did not increase as much as crude prevalence (1.90% in 2014 (reference), 1.84% in 2015, 1.91% in 2016, and 2.09% in 2017). Analysis of 5-year age groups revealed that the prevalence of NVAF increased in the older age groups for both men and women (Figure 1), with a higher prevalence in men than in women in all age groups. In particular, the prevalence of NVAF in males aged 70–74 years increased year on year.

Patient Characteristics in Each Year

Patient characteristics in each year from 2014 to 2017 are summarized in Table 1. Approximately 70% of subjects were men, and the proportion of those aged ≥65 years increased slightly year on year (72%, 77%, 82%, and 79% in 2014, 2015, 2016, and 2017, respectively). Over this period, no major changes were observed in CHADS2 scores or the frequency of comorbidities (heart failure, hypertension, diabetes, and a history of previous stroke/TIA). Notably, approximately 80% of patients had hypertension in all years.

Prescription Rates for OAC and DOACs

Prescriptions of OAC increased over the 4 years, from 72% in 2014 to 78% in 2017 (Figure 2; Ptrend<0.005). The proportion of NVAF patients prescribed warfarin decreased year on year (42%, 33%, 24%, and 21% in 2014, 2015, 2016, and 2017, respectively; Ptrend<0.0001), with the proportion of

national survey carried out every 10 years in 1980, 1990, and 2000,18 the report of Inoue et al based on annual health examinations in 2006,2 and the report of Iguchi et al from a public health center-based screening health test in 2008.1 Because the diagnosis of AF in these 3 studies was based on electrocardiogram (ECG) examinations, both valvular AF and NVAF patients were included.

OAC Prescription and Annual Trends

The study patients who were receiving OAC therapy were classified into 3 groups: a no-OAC group, a warfarin group, and a DOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) group. The number of patients in each of these 3 groups was compared in each year from 2014 to 2017. Age, sex, comorbidities (heart failure, hypertension, diabetes, and a history of previous stroke/TIA), and the CHADS2 score, which is scored according to whether a patient has congestive heart failure, hypertension, age ≥75 years, diabetes, and a history of previous stroke/TIA,19 were evaluated in each group.

Statistical Analysis

Group data are presented as numbers and percentages or as the mean±SD, as appropriate. the Shapiro-Wilk test was used to test the normality of all distributions. Comparisons between groups were performed using the Chi-squared test for categorical variables and the Mann-Whitney U-test for continuous variables. The Cochran-Armitage trend test was used to examine temporal trends in OAC prescriptions over time.14 P<0.05 was considered significant. Statistical analyses were conducted using JMP Pro version 12 (SAS institute, Cary, NC, USA).
those prescribed DOACs increasing gradually over the same period (30%, 42%, 50%, and 57%, respectively; $P_{\text{trend}}<0.0001$) and the proportion not prescribed an OAC decreasing gradually (28%, 25%, 26%, and 22%, respectively; $P_{\text{trend}}<0.005$).

Regardless of patients’ CHADS$_2$ scores, the trends for the proportion of NVAF patients prescribed warfarin and DOACs and not prescribed an OAC were similar (Figure 3): the proportions of those prescribed warfarin and not prescribed OAC decreased, whereas the proportion of those prescribed DOACs increased. In the patient groups with CHADS$_2$ scores of 1 and ≥2, the proportion not prescribed an OAC decreased gradually over the 4 years. However, in 2017, the proportion of patients not prescribed an OAC was still 31% (96/311) in the group with a CHADS$_2$ score of 1 (n=311) and 17% (132/758) in the group with a CHADS$_2$ score ≥2 (n=758; Figure 3). In 2017, 660 patients were prescribed DOACs. Among these patients, 12% were...
Comparison of NVAF or AF Prevalence and Comorbidities Among Studies

The overall prevalence of NVAF in 2017 in the present study was higher than the prevalence of AF (including valvular AF and NVAF) reported previously in Japan, especially in those aged ≥65 years (Table 3). Furthermore, approximately 80% of patients in the present study had prescribed dabigatran, 43% were prescribed rivaroxaban, 27% were prescribed apixaban, and 18% were prescribed edoxaban.

We compared age, sex, CHADS2 scores, and comorbidities among the no-OAC, DOACs, and warfarin groups according to the 2017 data (Table 2). Patients in the no-OAC group were younger and had a lower CHADS2 score than those in the DOACs and warfarin groups. Regarding comorbidities, heart failure and a history of previous stroke/TIA were less frequent in the no-OAC group than in DOACs and warfarin groups, whereas the rates of hypertension and diabetes were similar among the 3 groups. Although the mean CHADS2 score was slightly lower in the DOACs than warfarin group (2.21±1.28 vs. 2.30±1.19) and the prevalence of heart failure was lower in the DOACs group, there were no major differences in patient characteristics between the DOACs and warfarin groups.

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hypertension, compared with only 40% in the previous studies, and approximately 40% of patients in the present study had diabetes, compared with only 20% in the previous studies.\textsuperscript{1,2,18}

**Discussion**

**Major Findings**

The present study is the first to examine trends in NVAF prevalence and OAC therapy in a Japanese region using data obtained from the KDB. We found that the prevalence of NVAF in the Tsugaru region increased gradually over the 4-year study period and was higher than that reported previously in Japan, especially in subjects aged $\geq$ 65 years. In recent years, DOACs have taken the place of warfarin for NVAF patients. However, 17% of patients at high risk of stroke (CHADS\textsuperscript{2} score $\geq$2) were not prescribed an OAC in 2017.

**Prevalence of NVAF and Comparison With Previous Studies**

Although the prevalence of NVAF in the Tsugaru region increased gradually over the 4-year study period, the age-adjusted prevalence did not show a similar increase. These findings indicate that changes in the age distribution of the KDB subscribers in this region from 2014 to 2017, with a decrease in younger (40–64 years) subscribers and an increase in older (65–74 years) subscribers, may have affected the results.

In this study the prevalence of NVAF was almost 2.0% for each year; this was greater than that reported in previous studies (Table 3).\textsuperscript{1,2,18} There are several possible reasons for the high prevalence of NVAF in the present study. First, comorbidities can influence the prevalence of NVAF. The patients in the present study had more comorbidities than those included in previous studies, especially hypertension and diabetes, both of which are significantly associated with a higher incidence of NVAF.\textsuperscript{2,20} A relatively high CHADS\textsuperscript{2} score (mean 2.12) supports this finding. Furthermore, Kodani et al reported that the prevalence of AF in the TAMA MED Project-AF in Japan increased from 0.8% to 1.4% between 2008 and 2015, and in men from 1.7% to 2.9%, possibly due to an increase in comorbidities such as hypertension, diabetes, and metabolic syndrome.\textsuperscript{21} The findings of that study are consistent with the findings of the present study. A second possible factor affecting the prevalence of NVAF determined could be differences in data sources. In the present study we identified patients with AF from the KDB, whereas the other studies used data from a national survey, an annual health examination, or a public health center-based screening health test.\textsuperscript{1,2,18} The diagnosis of AF in those studies was based on ECG examinations, and so the number of patients with paroxysmal AF may have been underestimated. Despite these differences, the trend in sex differences in the present study was similar to that reported in the previous studies (i.e., the prevalence of NVAF was significantly higher in men than in women aged $\geq$ 245 years).\textsuperscript{1,2,4,18} This consistency among studies may support the reliability of our database and analysis.

**Trends in OAC Prescriptions**

Over the 4-year study period, the proportion of NVAF patients prescribed warfarin as OAC therapy decreased (from 58% in 2014 to 26% in 2017), whereas the proportion prescribed DOACs increased (from 42% to 74%; $P_{\text{trend}}$ $<$ 0.0001). Although warfarin was still the main drug used to prevent ischemic stroke in NVAF patients in 2014 in the Tsugaru region, DOACs had substantially taken the place of warfarin by 2017, becoming the main OAC treatment. Moreover, the proportion of patients receiving OAC and DOAC therapy (75% and 42%, respectively) in 2015 in the Tsugaru region was higher than that based on data from the Fushimi AF registry (64% and 26%, respectively).\textsuperscript{16} The mean age of patients in the Fushimi AF registry was 74 years, and 54% of patients were $\geq$ 75 years old;\textsuperscript{16,22} therefore, differences in the age distribution between the 2 studies may have affected the management of OAC therapy.

The increase in the proportion of DOAC prescription seems to be related to the advantages of DOACs compared with warfarin. Several meta-analyses have shown that DOACs treatment reduces not only stroke and systemic embolism events, but also intracranial hemorrhage and mortality compared with warfarin.\textsuperscript{23,24} Furthermore, functional outcome at discharge in patients with cardioembolic stroke that occurred during DOACs treatment was significantly improved compared with that of patients without OAC treatment.\textsuperscript{25,26} Regarding intracerebral hemorrhage, we previously reported that rivaroxaban was associated with relatively smaller hematomas and more favorable outcomes than warfarin in patients at high risk of bleeding.\textsuperscript{27} Together, these findings indicate that DOACs treatment appears to have potential benefits not only for the incidence of events, but also for functional outcome after both cardioembolic stroke and intracerebral hemorrhage in patients with NVAF. Furthermore, DOACs do not require routine coagulation monitoring and have shorter half-lives, resulting in earlier onset and elimination of action compared with warfarin. In contrast, warfarin requires adjustment of the prothrombin time (PT) and International Normalized Ratio (INR). A low INR is associated with an increased incidence of cardioembolic stroke and systemic embolism events, whereas a high INR is associated with a higher risk of a bleeding event. Importantly, the Fushimi AF registry previously showed that only 54.4% of patients receiving warfarin therapy had a PT/INR within the optimal therapeutic range at the time of enrollment,\textsuperscript{28} indicating the difficulty in controlling warfarin within the therapeutic range. Such information of the benefits of DOACs over warfarin may have affected physician’s decision making for OAC therapy. This was seen particularly in patients at high risk of thromboembolism: when classified by CHADS\textsuperscript{2} score, the proportion of NVAF patients receiving DOACs treatment increased from 31% in 2014 to 52% in 2017 in those with a CHADS\textsuperscript{2} score 1, and from 30% in 2014 to 60% in 2017 in those with a CHADS\textsuperscript{2} score $\geq$ 2 (Figure 3).

It should be pointed out that although the proportion of patients in the no-OAC treatment group decreased gradually among NVAF patients with a CHADS\textsuperscript{2} score of 1 and $\geq$ 2, 31% of those with a CHADS\textsuperscript{2} score of 1 and 17% of those with a CHADS\textsuperscript{2} score of $\geq$ 2 in 2017 still did not receive OAC therapy. The reason for this underuse of OAC therapy is unclear, but it is an important issue that remains to be resolved in a real-world setting. Conversely, not many, but some AF patients with a CHADS\textsuperscript{2} score of 0 were receiving OAC therapy, possibly because these patients had a risk factor based on the CHADS\textsuperscript{2}:VASC score.\textsuperscript{29}
Study Limitations
This study has several limitations. First, the study was a retrospective observational study restricted to the Tsgaru region of Aomori Prefecture in Japan. Therefore, caution should be exercised before applying the results to a general population. Second, the study enrolled only KDB subscribers, which may have resulted in selection bias. In addition, because subjects aged ≥75 years were not registered in the KDB database, we were not able to obtain and analyze their data. However, the KDB coverage rate in this study increased gradually with increasing age: 20–40% in those <60 years, 55% in those ≥60 years, and ≥69% in those ≥65 years (Supplementary Table). Because the incidence of AF was shown to increase in those ≥60 years,2 the high KDB coverage rate in those ≥60 years in the present study may minimize this limitation. Furthermore, although generally the number of patients who decline to participate in registry studies, such as the J-RHYTHM Registry and the Fushimi AF Registry, cannot be evaluated, because the data of all patients registered in the KDB are basically available, the number of patients who declined to take part in the present study could be determined (6 patients refused to allow the use of their data in the present study). That is, by using the KDB, we can assess all the patients in a region, including the current status of OAC use and even possible future events, if patients are longitudinally followed-up. This may be one of the important advantages for the use of the KDB. Finally, we could not verify in detail other risk factors for NVAF, such as obesity and smoking, or calculate the HAS-BLED score (the risk score for major bleeding),19 because the KDB does not store data regarding alcohol consumption and renal function.

Conclusions
We studied trends in NVAF prevalence and OAC therapy in a Japanese region using data obtained from the KDB. The prevalence of NVAF increased gradually from 2014 to 2017. The prescription of DOACs increased and that of warfarin decreased over the 4-year study period in the Tsgaru region in Japan.

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Conflict of Interest
H. Tomita has received research funding from Boehringer Ingelheim, Bayer, Daiichi-Sankyo, and Pfizer, and Speakers Bureau/Honoraria from Boehringer Ingelheim, Bayer, Daiichi-Sankyo, and Bristol-Myers Squibb. Ken Okumura has received Speakers Bureau/Honoraria from Boehringer Ingelheim, Bayer, and Daiichi-Sankyo. The remaining authors have no relevant disclosures.

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**Supplementary Files**

Please find supplementary file(s):
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