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ORIGINAL ARTICLE
Miscellaneous

Serial changes in the trends of direct oral anticoagulant use and incidence of thromboembolisms and major bleeding events in very old patients with non-valvular atrial fibrillation

Masahiko Takahashi[1], Takeshi Morimoto [2], Ryu Tsushima[1], Yuya Sudo[1], Ai Sakamoto[1], Masahiro Sogo[1], Masatomo Ozaki[1], and Keisuke Okawa [1,*]

[1]Department of Cardiovascular Medicine, Kagawa Prefectural Central Hospital, 1-2-1 Asahi-machi, Takamatsu, Kagawa 760-8557, Japan; and [2]Department of Clinical Epidemiology, Hyogo Medical University, 1-1 Mukogawa, Nishinomiya, Hyogo 663-8501, Japan

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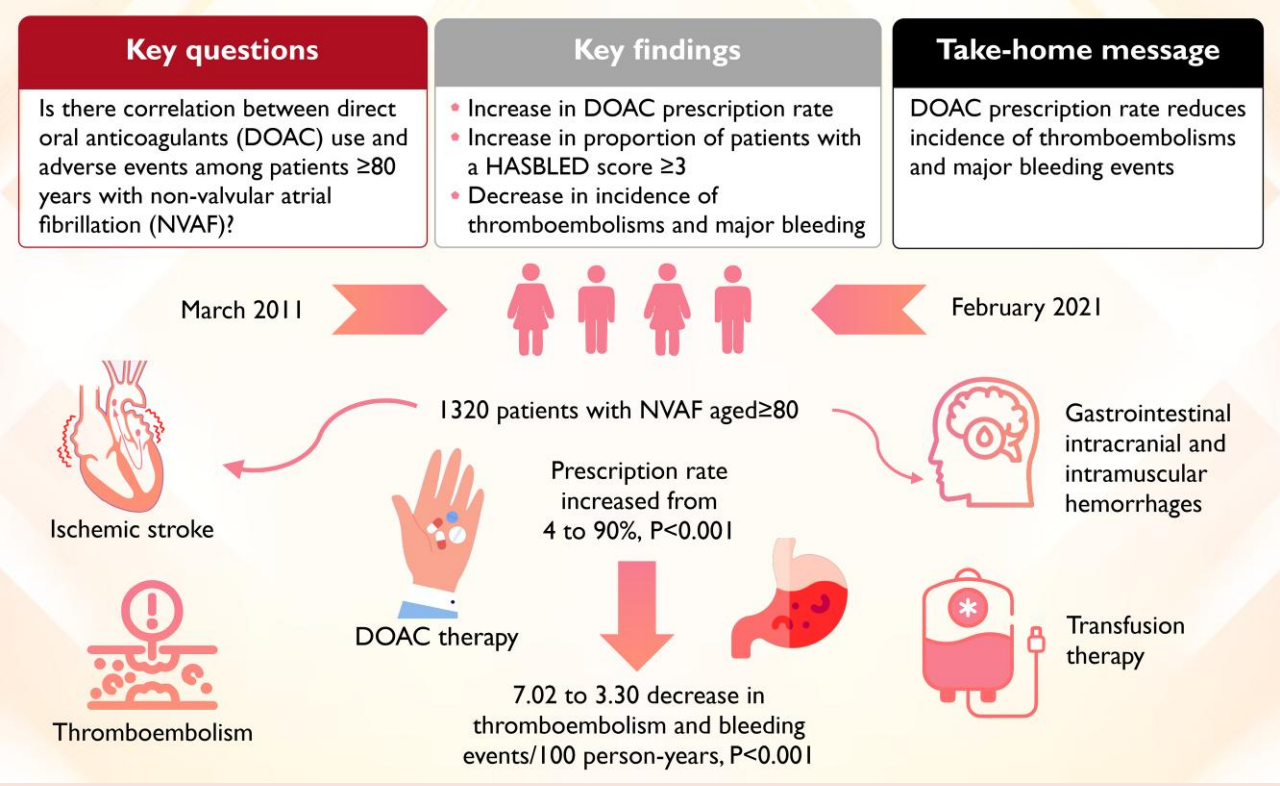
Aims Direct oral anticoagulants (DOACs) have become the first-line antithrombotic therapy in patients with non-valvular atrial fibrillation (NVAF). During this period, the incidence of thromboembolisms and major bleeding events has decreased. However, no studies have shown a correlation between them, and even fewer data are available on older patients. Therefore, we evaluated the serial changes in oral anticoagulant (OAC) use and the correlation between DOAC use and the incidence of adverse events among very old patients with NVAF.

Methods and results We conducted a historical cohort study in 1320 consecutive patients with NVAF aged ≥80 years who received medical treatment for AF from March 2011 to February 2021. We analysed the temporal trends regarding patients using OACs, including the DOAC prescription rate and incidence of adverse events. Over the last decade, the number of patients using OACs has increased from 228 to approximately 600 person-years. The DOAC prescription rate has significantly increased (4–90%, $P < 0.001$). The age of the patients and proportion of patients with a HASBLED score ≥3 significantly increased (84 ± 4 to 86 ± 4 years, 16–25%, $P < 0.001$, respectively). The composite incidence of thromboembolisms and major bleeding events significantly decreased (7.02–3.30 events/100 person-years, $P < 0.001$).

Conclusion The incidence of thromboembolisms and major bleeding events might be inversely correlated with the increase in the DOAC prescription rate in patients with NVAF aged ≥80 years.

* Corresponding author. Tel: +81 87 811 3333, Email: k-ookawa@chp-kagawa.jp

Graphical Abstract



Keywords Atrial fibrillation • Direct oral anticoagulant • Major bleeding • Thromboembolism • Old patients

Introduction

Antithrombotic therapy, which is fundamental in the management of patients with atrial fibrillation (AF), is particularly important for older people because the risk of thromboembolisms and major bleeding events increases with age.[1,2] Over the past decade, direct oral anticoagulant (DOAC) use as a first-line antithrombotic therapy in patients with non-valvular atrial fibrillation (NVAF) has been promoted based on the accumulated evidence of the efficacy and safety of DOACs compared to warfarin in landmark randomized clinical trials and many observational studies.[3–7] Recent studies have shown that DOACs have preventive effects on not only thromboembolisms and major bleeding events but also all-cause mortality in older people.[8,9] Per available evidence,[10,11] in the first decade since the launch of DOACs, the incidence of thromboembolisms and major bleeding events has been presumed to have decreased along with the increase in DOAC prescriptions.

However, information on the real-world trends in antithrombotic therapy and outcomes among older patients is limited. Therefore, we investigated the trend in the use of DOACs during the first decade since their launch and the incidence of thromboembolisms and major bleeding events in patients with NVAF who were aged ≥80 years during the same period. We further evaluated the correlation between the DOAC prescription and incidence rate of adverse events among very old patients with NVAF.

Methods

Study design and patients

We conducted a historical cohort study of consecutive patients with non-valvular AF aged ≥80 years who received medical treatment for AF from March 2011 to February 2021 at Kagawa Prefectural Central Hospital, Kagawa, Japan. The inclusion criteria were as follows: (i) a diagnosis of AF, including both new and existing diagnoses that were based on electrocardiogram recordings in our hospital at the time of the hospitalization or outpatient clinic visits due to not only AF itself but also coexisting diseases. (ii) An age ≥80 years at the time of enrolment. The exclusion criteria were as follows: (i) valvular heart disease, (ii) end-stage renal failure, creatinine clearance <15 mL/min/1.73 m^2, or regular dialysis, and (iii) non-use of OACs. Valvular heart disease was defined as moderate or severe mitral stenosis or a mechanical valve replacement.

We determined the first observation day of the study based on the patient's age and anticoagulant use. The first observation day was defined as one of the following: (i) the start date of the study (1 March 2011) for patients who were aged ≥80 years and were using anticoagulants at the time, (ii) the 80th birthday for patients aged <80 years who were using anticoagulants on the start date of the study, and (iii) the anticoagulation therapy start date for patients that did not use anticoagulants before.

This study conformed to the principles of the Declaration of Helsinki and was conducted with the approval of the Clinical Ethics Committee of the Kagawa Prefectural Central Hospital. Written informed consent was substituted by an opt-out method by announcing the handling of

personal data and the right to withdraw consent on the website of the study institution.

Data collection and variables

We collected data on the patient characteristics, including the medical history, laboratory data, medication use, electrocardiography findings, and transthoracic echocardiography findings from electric medical records. We used the CHA_2DS_2-VASc score for the risk stratification of ischaemic strokes or systemic embolisms[12] and the HASBLED score for the risk stratification of bleeding.[13] We used the modified HASBLED as the original HASBLED score minus the labile time in the therapeutic range (TTR) in this study because a labile TTR would be present only for warfarin use. We calculated the TTR as an index of the warfarin control using Rosendaal's linear interpolation method.[14] We set the target international normalized ratio at 1.6–2.6 for older patients based on the Japanese guidelines.[15] We included the following four types of DOACs: dabigatran, rivaroxaban, apixaban, and edoxaban. We investigated the outcomes primarily from the electric medical records at Kagawa Prefectural Central Hospital. We further investigated the outcomes in March 2021 by a mail-in questionnaire or telephone call to the patients, families, and their primary care physicians for those who completed the clinical visits at Kagawa Prefectural Central Hospital. We investigated the stop date of the anticoagulant therapy from the description in the medical records at the hospitals, prescription records, and mail-in questionnaires that had a description column for the duration of the anticoagulation.

Study outcomes

The primary outcome was the annual composite incidence of both thromboembolisms and major bleeding events. The secondary outcome was the annual incidence of thromboembolisms and major bleeding events. We defined a thrombo-embolic event as an ischaemic stroke (including transit ischaemic attack) and systemic embolism. We defined a major bleeding event as an intracranial haemorrhage, gastrointestinal haemorrhage, intramuscular haemorrhage/haematoma, and other forms of haemorrhage requiring a transfusion or hospitalization that met a Bleeding Academic Research Consortium criteria ≥2.[16]

Statistical analysis

We censored observations due to (i) a loss to follow-up by the end date of the study (28 February 2021) and (ii) discontinuation of anticoagulant treatment. We continued to observe the patients after the thromboembolism and major bleeding events. When the patient switched the oral anticoagulant (OAC) from a DOAC to warfarin or from warfarin to a DOAC, we changed them to another OAC group and continued to observe them. When the patients changed the dose setting or the type of DOAC, we also continued to observe them. We excluded any observation of an OAC that was switched and immediately discontinued due to poor tolerance.

We expressed the patient characteristics, including the DOAC use and catheter ablation of AF, for each year in person-years, and the number of events in 100 person-years. The patient characteristics were evaluated on the observational start date each year (March 1st) or on the newly registered date. Continuous variables are expressed as the mean and standard deviation while categorical variables are presented as frequencies and percentages. We evaluated the trends in the patient characteristics, DOAC prescription rate, and event rate using the Jonckheere-Terpstra trend test over 10 years. The characteristics that changed significantly over the decade were further evaluated, including the changes in the detailed distribution.

As a subgroup analysis, we investigated the trend in the primary outcome in the patients with a CHA_2DS_2-VASc ≥5 and those with a modified HASBLED score ≥3, respectively, to evaluate the trend in the higher-risk patients uncovered in the previous randomized trials of DOACs. As a sensitivity analysis, we investigated the trend in the primary outcome excluding the patients who underwent AF ablation both before and after the study observation period to eliminate the effect of AF ablation. As an additional analysis, we investigated the annual percentage of patients not taking or discontinuing OACs and the primary outcome among them and compared the trend in the primary outcome to that in the patients taking OACs by plotting them on the same graph.

Two-sided *P*-values of <0.05 were considered statistically significant. All statistical analyses were performed using SPSS Statistics version 28 software (IBM Institute Inc., Chicago, IL, USA).

Results

Between March 2011 and February 2021, 1320 patients with NVAF were identified. Of those, 132 switched OACs from warfarin to a DOAC based on the consideration of poor adherence and the risk of warfarin. Among them, seven patients re-switched OACs from a DOAC to warfarin. All of them restarted warfarin within a few days due to poor tolerance to the DOACs; therefore, the observation of the DOAC prescription period was excluded, and the warfarin prescription period continued. As a result, there were no patients who switched anticoagulants from a DOAC to warfarin. The number of patients who were lost to follow-up within the observation period was 71 (5.4%), and the number of those who discontinued anticoagulants was 43 (3.3%). The reasons for the discontinuation of anticoagulant treatment included minor bleeding ($n = 13$), aging ($n = 2$), a decline in the renal function ($n = 2$), poor adherence or warfarin control ($n = 3$), an invasive procedure ($n = 7$), and unknown ($n = 16$).

The annual changes in the patient characteristics are shown in *Table 1*. The number of patients using OACs increased to approximately 600 person-years.

The age increased over the decade (84 ± 4 to 86 ± 4 years). The proportion of patients aged ≥85 years, especially those aged ≥90 years, increased to more than 60% (see Supplementary material online, *Figure S1*). The proportion of female patients increased slightly (46–49%). The proportion of patients with paroxysmal AF increased (26–55%) (see Supplementary material online, *Figure S1*). The body weight and creatinine clearance of the patients increased slightly (53 ± 11 to 56 ± 11 kg, 45 ± 17 to 48 ± 16 mL/min kg, respectively). The proportion of patients with a higher body weight (≥60 kg) or creatinine clearance (≥60 mL/min) increased, whereas that of those with a lower body weight (≤50 kg) and creatinine clearance (≤50 mL/min) decreased (see Supplementary material online, *Figure S2*). For the risk factors, the proportion of patients with hypertension increased (60–73%), whereas that of those with heart failure decreased (47–41%), and those with diabetes mellitus did not change (19–19%). The proportion of patients with a history of thromboembolisms or major bleeding events decreased (30–17%, 6–4%). For the risk scores, the proportion of patients with a CHA_2DS_2-VASc score ≥5 decreased (47–42%), whereas that of those with a HASBLED score ≥3 increased (16–25%). For the detailed risk scores, the proportions of patients with CHA_2DS_2-VASc scores of 3–5 and those with HASBLED scores of 2 and 3 increased (see Supplementary material online, *Figure S3*).

The DOAC prescription rate increased (4–90%). For the detailed anticoagulant use, the prescription of a low-dose DOAC, mostly within an appropriate dose setting, increased to 75%. Although the number of patients with poor control of their warfarin use (TTR <60%) decreased overall, the proportion of patients with a TTR <60% did not change. Among the types of DOACs, the apixaban and edoxaban prescription rates increased from their launch (up to 47% for apixaban and 20% for edoxaban) (see Supplementary material online, *Figure S4*). The proportion of patients who underwent AF ablation increased (0–3%).

The trends in the incidence of thromboembolisms and major bleeding events over the decade are shown in *Figure 1* along with the trends in the DOAC prescription rate. The composite incidence of thromboembolisms and major bleeding events as a primary outcome decreased (7.02 events/100 person-years to 3.30 events/100 person-years, $P < 0.001$). As secondary outcomes, the incidence of thromboembolisms and that of major bleeding events decreased significantly (thromboembolism: 3.07 events/100 person-years to 1.26 events/100 person-years,

Table 1 Patient characteristics for each year

	2011/3 –2012/2	2012/3 –2013/2	2013/3 –2014/2	2014/3 –2015/2	2015/3 –2016/2	2016/3 –2017/2	2017/3 –2018/2	2018/3 –2019/2	2019/3 –2020/2	2020/3 –2021/2	*P*
Under observative patients, *N*	228	296	357	402	470	543	602	639	656	637	—
Age, years, mean (SD)	84 (4)	84 (4)	85 (4)	85 (4)	85 (4)	86 (4)	86 (4)	86 (4)	86 (4)	86 (4)	<0.001
Female patients, *N* (%)	105 (46)	136 (46)	164 (46)	189 (47)	225 (48)	266 (49)	307 (51)	326 (51)	328 (50)	312 (49)	0.03
Paroxysmal AF, *N* (%)	58 (26)	83 (28)	104 (29)	144 (36)	202 (43)	249 (46)	283 (47)	321 (50)	355 (54)	350 (55)	<0.001
Body weight, kg mean (SD)	53 (11)	53 (11)	54 (11)	54 (11)	54 (11)	54 (11)	54 (11)	55 (11)	56 (11)	56 (11)	<0.001
Creatinine clearance, mL/min, mean (SD)	45 (17)	45 (17)	46 (17)	46 (17)	46 (17)	46 (17)	47 (17)	47 (17)	48 (17)	48 (16)	<0.001
Heart failure, *N* (%)	107 (47)	126 (43)	152 (43)	161 (40)	196 (42)	227 (42)	247 (41)	273 (43)	278 (42)	259 (41)	0.25
Hypertension, *N* (%)	137 (60)	188 (63)	232 (65)	266 (66)	316 (67)	383 (70)	432 (72)	467 (73)	476 (73)	465 (73)	<0.001
Diabetes mellitus, *N* (%)	44 (19)	57 (19)	72 (20)	82 (21)	96 (21)	114 (21)	124 (21)	133 (21)	125 (19)	119 (19)	0.93
History of a thromboembolism, *N* (%)	68 (30)	92 (31)	111 (31)	114 (29)	124 (26)	131 (24)	135 (22)	137 (21)	125 (19)	111 (17)	<0.001
History of major bleeding, *N* (%)	13 (6)	15 (5)	21 (6)	24 (6)	29 (6)	32 (6)	31 (5)	32 (5)	28 (4)	25 (4)	0.03
Antiplatelet drug use, *N* (%)	58 (25)	72 (24)	86 (24)	103 (26)	113 (24)	125 (23)	136 (23)	145 (23)	153 (23)	144 (23)	0.02
CHA_2DS_2-VASc ≥5, *N* (%)	107 (47)	139 (47)	174 (49)	191 (48)	219 (47)	249 (46)	282 (47)	303 (47)	297 (45)	269 (42)	0.09
HASBLED ≥3, *N* (%)	35 (16)	51 (18)	65 (19)	81 (22)	100 (23)	124 (25)	147 (26)	116 (28)	167 (27)	151 (25)	<0.001
DOAC prescription, *N* (%)	10 (4)	40 (14)	77 (21)	146 (36)	250 (53)	364 (67)	454 (75)	532 (83)	576 (88)	571 (90)	<0.001
Catheter ablation of AF, *N* (%)	0 (0)	0.7 (0.2)	0.2 (0.05)	5 (1)	8 (2)	22 (4)	20 (3)	24 (4)	36 (6)	22 (3)	0.003

Values are presented as the mean (SD) and the person-years of the patients (%).
AF, atrial fibrillation; DOAC, direct oral anticoagulant; N, person-year; SD, standard deviation.

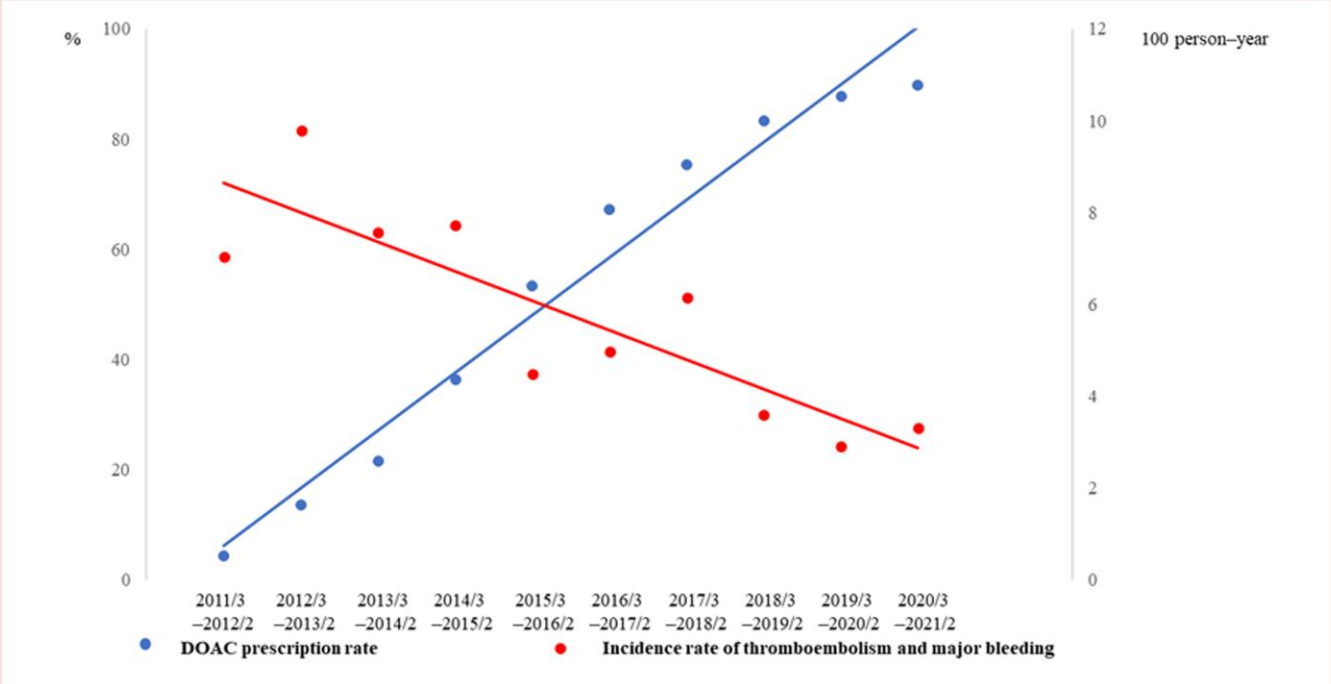


Figure 1 Trend in the direct oral anticoagulant prescription rate and incidence of thromboembolisms and major bleeding events. The annual composite incidence of thromboembolisms and major bleeding events (100 person-years) decreased over the decade. The direct oral anticoagulant prescription rate increased. DOAC, direct oral anticoagulant.

P = 0.006, major bleeding events: 3.95 events/100 person-years to 2.04 events/100 person-years, *P* = 0.09) (*Figure 2A and B*).

The subgroup analyses among the patients with a CHA_2DS_2-VASc ≥5 and those with a modified HASBLED score ≥3 revealed consistent results to the main analysis, respectively (see Supplementary material online, *Figure S5A and B*). The number of patients with a history of AF ablation was 98, and that in those who underwent AF ablation during the study observation period was 200. The sensitivity analysis

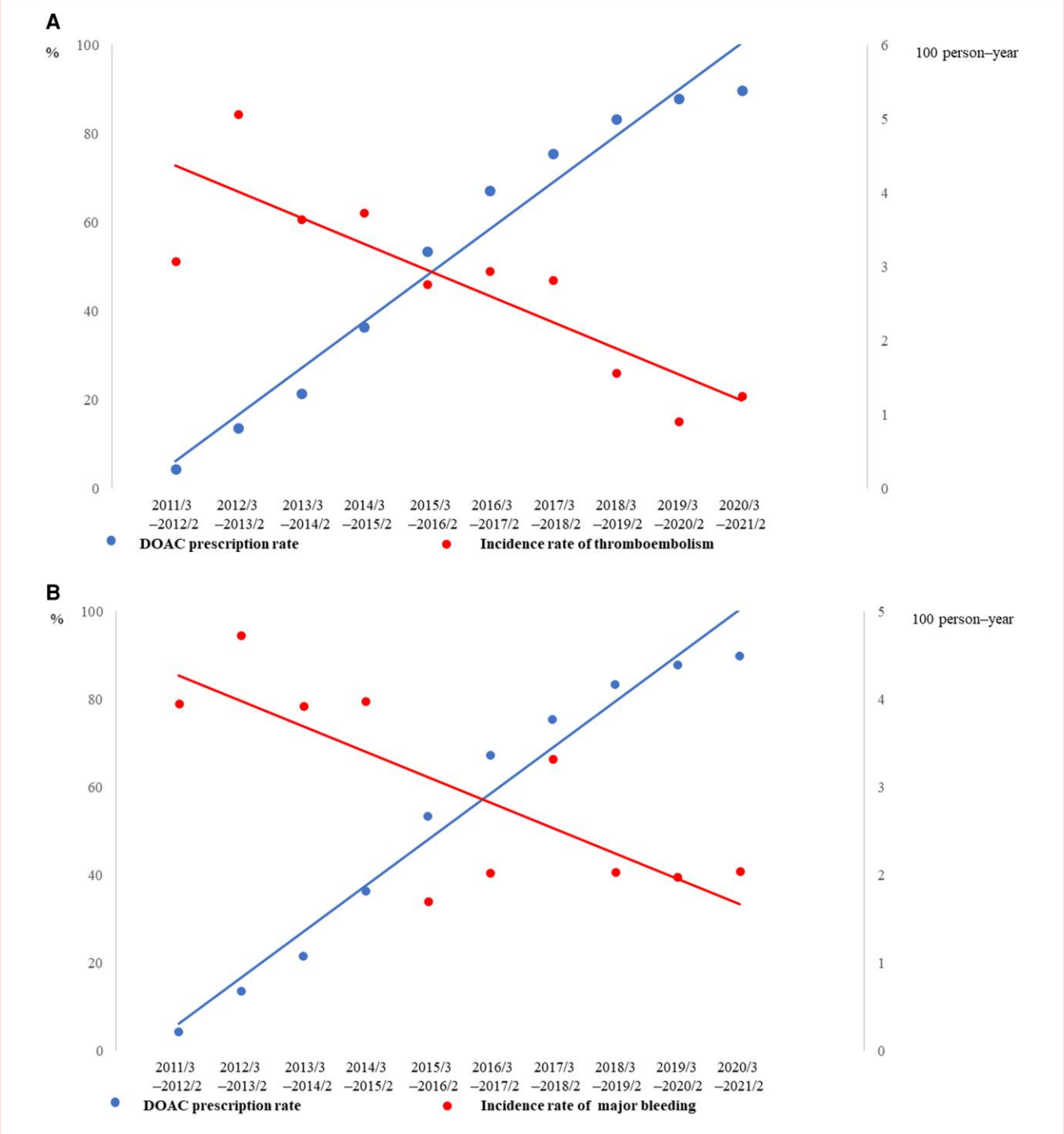


Figure 2 (*A*) Trend in the direct oral anticoagulant prescription rate and incidence of thromboembolisms. The annual incidence of thromboembolisms (100 person-years) decreased over the decade while the direct oral anticoagulant prescription rate increased. DOAC, direct oral anticoagulant. (*B*) Trend in the direct oral anticoagulant prescription rate and incidence of major bleeding events. The annual incidence of major bleeding events (100 person-years) decreased over the decade. The direct oral anticoagulant prescription rate increased. DOAC, direct oral anticoagulant.

excluding the 298 patients who underwent AF ablation revealed consistent results to the main analysis (see Supplementary material online, *Figure S6*). The percentage of patients not taking OACs rapidly decreased over the decade. The annual incidence of thromboembolisms and the major bleeding event rate among them was consistently high, however, that varied from year to year due to the low number of patients. At the beginning of the study observation, the event rate was higher in the patients taking OACs than in those not taking OACs; however, that became inversed over the decade (see Supplementary material online, *Figure S7*).

Discussion

The temporal trends in antithrombotic therapy after the introduction of DOACs have been indicated in several studies[17–19]; however, there is a paucity of data on the older population. A nationwide study in Taiwan that investigated very old (≥85 years) patients with newly diagnosed AF from 2009 to 2015 reported that the initiation rates of OACs significantly increased from 9.5% to 34.3% after the introduction of DOACs (DOACs: 0–26.2%).[20] The study also revealed that the 1-year risk of an ischaemic stroke and mortality decreased with the increase in the rate of an OAC prescription; however, the 1-year risk of an intracranial haemorrhage remained unchanged.[20] Our study confirmed the increase in the number of OAC prescriptions and the decrease in the incidence of thromboembolisms over the decade after the introduction of DOACs and further clarified the decrease in the rate of major bleeding events and the association between the DOAC prescription rate and composite outcomes of thromboembolisms and major bleeding events. Our findings can be explained by the rapid increase in the number of patients using OACs as well as the DOAC prescription rate (which ultimately reached up to 90% for patients on OACs).

As shown by the increasing trend in the age, CHA_2DS_2-VASc score, and HASBLED score, antithrombotic therapy appeared to be common among patients with a higher risk of a thromboembolism and bleeding. In contrast, the increase in the proportion of patients with a higher body weight and creatinine clearance values and paroxysmal AF suggested that antithrombotic therapy using DOACs was also common among more healthy patients without frailty and advanced AF. Moreover, the decrease in the proportion of patients with a lower body weight and creatinine clearance value should be reflected, as these factors are becoming recognized and paid attention to as a higher bleeding risk of DOACs among the older population. These changes in the patient background could indicate both a lowering of the indication threshold of antithrombotic therapy and refining the DOAC use, even among older people, along with the individuals' experiences.

Regarding the decrease in the incidence of thromboembolisms and major bleeding events over the decade, multiple factors other than the DOAC prescription rate or differences in the patient background should be considered, including the advancement in the medical treatment and improvement in the level of awareness of the patients, their families, and primary care physicians. Even considering those, we are convinced that the spread in the DOAC use among older people was associated with the decrease in the rates of thromboembolisms and major bleeding events because many studies, including ours, have reported the preventive effect of DOACs on thromboembolisms and major bleeding events as compared to that of warfarin in older patients.[8,9,21–23] Advances in catheter ablation of AF over the decade have been notable even for older people. In fact, the annual number of AF ablation procedures has gradually increased in this cohort. However, the annual number of patients who underwent AF ablation was relatively small, and the trend in the incidence of thromboembolisms and major bleeding events also significantly decreased over the decade among the patients who did not undergo AF ablation.

Our study demonstrated that the DOAC prescription rate rapidly increased to 90% among very old patients with NVAF in the first decade since their launch. In addition, we confirmed that the incidence of thromboembolisms and major bleeding events decreased with the increase in DOAC prescriptions. Notably, the incidence of major bleeding events decreased despite the increase in the use of OACs among patients with a high bleeding risk. The findings of this study could be helpful in determining appropriate antithrombotic therapy for older patients in daily clinical practice.

There were several limitations to the interpretation of the results of this study. First, this was a historical observational study regarding the trends in clinical practice at a single centre and the sample size was relatively small; however, the detailed clinical courses and outcomes could be well-captured because of the single-centre study design. The hospital where this study was performed is a leading centre for arrhythmic disorders covering more than one prefectural area and included 1 million people. Therefore, the results of this study reflect the typical advanced clinical practice in Japan. Second, patients who were not on anticoagulants were excluded. Although this selection bias could affect the results, there were various reasons for these patients to not consume anticoagulants, including non-tolerance to anticoagulants, because of adverse events and undiagnosed AF because they did not visit the hospital. Because of the difficulty associated with investigating all patients, only those on anticoagulants were included. Based on the limitation that the patients not taking OACs in our cohort reflected only a part of the patients not taking OACs, the event rate among them could be confirmed as being high over the decade as compared to that among those taking anticoagulants. Finally, the effect of unobserved factors, such as socioeconomic factors, was unavoidable. Global studies on older patients with AF should be conducted to verify the association between the DOAC prescription and event rates.

Conclusion

In the first decade of DOAC use, antithrombotic therapy with warfarin was rapidly replaced by DOACs in very old patients (≥80 years) with NVAF. The incidence of thromboembolisms and major bleeding events decreased with the increase in the DOAC prescription rate.

Lead author biography

Dr Masahiko Takahashi, MD, Department of Cardiology of the Kagawa Central Prefectural Hospital. He is Fellow of the Japanese Society of Internal Medicine, Board Certified Member of The Japanese Circulation Society, Board Certified Member of the Japanese Heart Rhythm Society, and Board Certified Member of the Japanese Association of Cardiovascular Intervention and Therapeutics. He has a proven track record of research on anticoagulation in older patients with atrial fibrillation.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

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Conflict of interest: Dr Takahashi reports lecture's fees from Bayer and Daiichi Sankyo. Dr Morimoto reports lecturer's fees from Bristol-Myers Squibb, Daiichi Sankyo, and Pfizer; manuscript fees from Bristol-Myers Squibb and Pfizer. Dr Okawa reports lecture fees from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, and Pfizer. The other authors have nothing to disclose.

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