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RESEARCH

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Underutilization of anticoagulants in patients with nonvalvular atrial fibrillation in the era of non-vitamin K antagonist oral anticoagulants

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Abstract

Background: Non-vitamin K antagonist oral anticoagulants (NOACs) are preferred over vitamin K antagonists (VKAs) as oral anticoagulant (OAC) therapy in patients with nonvalvular atrial fibrillation (NVAF). This study aimed to estimate the current status and risk factors of OAC underutilization in the NOAC era.

Method: A cross-sectional study using nationwide claims data was conducted. Elderly patients with NVAF at an increased risk of stroke were selected as candidates for OAC therapy before the index date (July 1, 2018). The status of anticoagulant utilization on the index date and factors influencing the use of anticoagulants was investigated in these patients.

Results: Of the 11,056 patients with NVAF who were eligible for OAC therapy, 7238 (65.5%) were receiving OAC on the index date, and 6302 (87.1%) were receiving NOACs. Patients aged ≥ 75 years had higher anticoagulant utilization than those aged 65–69 years. Among comorbid diseases, while hypertension was the most influential positive factor (odds ratio [OR] = 1.644; confidence interval [CI] = 1.445–1.869) in OAC utilization, severe renal disease was the most influential negative factor (OR = 0.289; CI = 0.200–0.416). Aspirin use had a significantly low OR (OR = 0.097; CI = 0.085–0.110) of anticoagulant use. OAC use was approximately 1.5 times higher in patients with persistent or permanent AF than in those with paroxysmal AF.

Conclusion: Approximately one-third of patients who are recommended anticoagulation therapy do not take OACs, even though the use of NOACs has become more common. It should be widely recognized that aspirin cannot be an alternative to OACs, and anticoagulant therapy should be actively implemented.

Keywords: Atrial fibrillation, Stroke, Anticoagulants, Warfarin, Non-vitamin K antagonist oral anticoagulants, Underutilization

Introduction

The prevalence of atrial fibrillation (AF) is rising worldwide due to an aging population and advances in diagnostic technology [1, 2]. In the USA, approximately 5.2 million individuals were affected by AF in 2010, and 12.1 million individuals have estimated to be affected by AF in 2030 [1, 3]. In South Korea, the prevalence of AF has been consistently increasing from 0.73% in 2006 to 1.53% in 2015 and is expected to reach 5.81% in 2060 [4]. AF is associated with a four–fivefold increased risk of ischemic stroke [5] and is known as an independent risk factor for ischemic stroke severity, recurrence, and mortality [6].

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For patients with AF and an elevated CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥ 75 years [doubled], diabetes mellitus, prior stroke or transient ischemic attack [TIA] [doubled], vascular disease, age 65–74 years, and sex) score, oral anticoagulants (OACs) are recommended because the risk of stroke can be greatly reduced by anticoagulation therapy [7–10]. However, the underutilization of anticoagulation therapy in patients with AF has been recognized as a global health problem [11–14].

OAC therapy for patients with AF has been limited to warfarin for a long time, and insufficient OAC option has been evaluated as a risk factor for OAC underutilization [15]. However, since the introduction of non-vitamin K antagonist oral anticoagulants (NOACs) in the 2010s, a range of OACs have become available for patients with AF. Moreover, NOACs are recommended over warfarin in NOAC-eligible patients with AF as it has non-inferior or superior efficacy and lower risk of serious bleeding than warfarin [7–10].

In South Korea, NOACs were considered second-line therapy in stroke prevention after the failure of warfarin due to contraindication, sensitivity, or treatment failure until July 2015. Currently, NOACs are used as first-line therapy. After February 2016, the following NOACs have been used dabigatran, rivaroxaban, apixaban, and edoxaban.

In a previous study, the rate of anticoagulant underutilization among patients with AF in South Korea was significant. Although it has been improving every year, it is considerably high [15, 16]. Female sex, old age, medical aid, and vascular disease have been identified as risk factors for anticoagulant underutilization [15]. NOACs have excellent efficacy in stroke prevention and are clinically useful for reducing the risk of bleeding. Further, dose adjustments are not needed for NOACs. Hence, the expansion of NOAC reimbursement criteria and diversification of drug choice is expected to improve the underutilization of anticoagulation therapy.

Several studies on the underutilization of anticoagulation therapy in patients with AF have been conducted, but the use of drugs was judged roughly, and most studies were conducted during the early stages of reimbursement criteria expansion [15–17]. Therefore, this study aimed to evaluate the current status and risk factors of OAC underutilization through cross-sectional analysis using real-world data.

Methods

Study data

Aged Population Sample (APS) data on approximately 700,000 individuals (10% extraction rate) aged ≥ 65 years in South Korea, collected by the Health Insurance Review and Assessment Service (HIRA) in 2018 (HIRA-APS-2018-0039), were used.

The Korean Classification of Diseases-7 codes (KCD-7 codes; the Korean version of ICD-10) was used to identify patients with specific diseases or conditions. Ingredient codes were used to identify four NOACs (dabigatran, rivaroxaban, apixaban, and edoxaban), warfarin, and aspirin ("Appendix").

The South Korean health insurance system consolidates all types of social insurance (the National Health Insurance [NHI], Medical Aid [MedAid], and Patriots & Veterans Insurance [PVI]) into a single-payer, and all citizens are obligated to subscribe to the system [18]. All types of social insurance are subject to the same benefit criteria but differ only in the patients' paying rate of healthcare costs for copayments. The NHI covers approximately 97% of the population and imposes a duty on income, while the MedAid is a guaranteed system for low-income people and the PVI is for national veterans [18]. The Institutional Review Board of the Pusan National University approved this study (PNU IRB/2020_92_HR).

Study subjects

Patients who were primarily diagnosed with AF or atrial flutter (AFL) between January 1, 2018, and June 30, 2018, were identified. Patients with valvular heart disease were excluded. Patients with mitral stenosis or valve replacement based on KCD-7 codes were classified as patients with valvular heart disease. Among patients with nonvalvular AF (NVAF), those who had a CHA_2DS_2-VASc score of ≥ 2 were considered appropriate candidates for anticoagulant therapy in this study. We investigated whether the study subjects were receiving OACs on the index date (July 1, 2018) and the types of OACs they were receiving.

The following factors influencing the use of anticoagulants were investigated: age, sex, insurance type, the presence of comorbid diseases, medical institution type, region, aspirin use, and AF type. Insurance types were divided into the NHI and MedAid/PVI. Comorbid diseases included congestive heart failure, hypertension, diabetes mellitus, stroke/TIA, vascular disease, anemia, severe renal disease, and prior hemorrhage. The medical institution types were divided into tertiary hospitals, general hospitals, and primary medical institutions. The region was divided into the capital city, six metropolitan cities, and other regions.

Statistical analysis

The patients' demographic characteristics are presented using frequency analysis and as percent, since all of them are categorical variables. The p values were determined using chi-squared tests for the anticoagulant utilization. We performed multiple logistic regression analysis to

analyze the factors affecting the anticoagulant utilization. The Hosmer–Lemeshow test was used to ensure the accuracy of the goodness of fit for the models. All statistical analyses were performed using R Statistical Software (version 4.1.1; R Foundation for Statistical computing, Vienna, Austria), and the significance level was set at $p < 0.05$.

Results

Subject characteristics

A total of 11,056 patients with NVAF requiring OAC therapy were included in the analysis on the index date (Fig. 1). The demographics and clinical characteristics of the study subjects are summarized in Table 1. Patients aged ≥ 75 comprised 56.0% of the study population, and the proportion of male patients was higher than that of female patients (52.0% vs. 48.0%). On the index date, 15.6% of patients were using aspirin.

Anticoagulants utilization rate

Of the 11,056 patients, 7,238 (65.5%) were receiving OACs on the index date. Among them, 6,302 (87.1%) patients were receiving NOACs. Rivaroxaban was the most commonly prescribed NOAC (32.9%), followed by edoxaban (28.0%), apixaban (26.9%), and dabigatran (12.3%).

Anticoagulant use increased with the increasing age, and anticoagulant use was lower in men than in women. Further, anticoagulant use was higher in patients with congestive heart failure, hypertension, diabetes mellitus, and stroke/TIA, whereas it was lower in patients with vascular disease, anemia, severe renal disease, and prior hemorrhage. The anticoagulant utilization rate was the highest in tertiary hospitals, followed by general hospitals and primary medical institutions/others. Furthermore, it was the highest in the capital city, followed by the six metropolitan cities and other regions. The anticoagulant utilization rate was significantly lower in patients

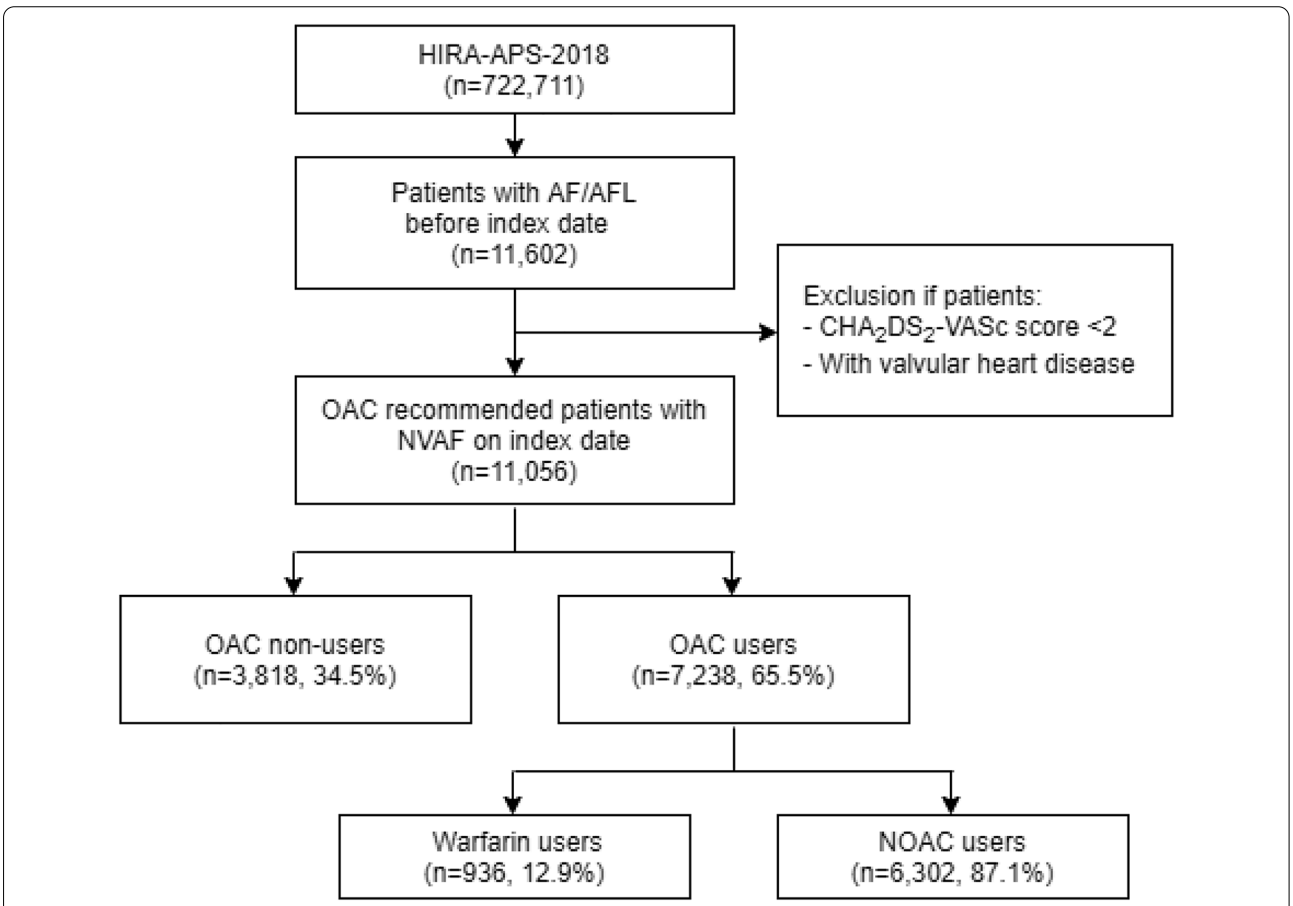

Fig. 1 Extraction of study subject. AF, atrial fibrillation; AFL, atrial flutter; CHA_2DS_2-VASc, congestive heart failure, hypertension, age of ≥ 75 years [doubled], diabetes mellitus, prior stroke or transient ischemic attack [TIA] [doubled], vascular disease, age of 65 to 74 years, and sex; HIRA-APS, Health Insurance Review & Assessment Service-Aged Population Sample; NOAC, non-vitamin K antagonist oral anticoagulant; NVAF, nonvalvular atrial fibrillation; OAC, oral anticoagulant

Table 1 Demographic characteristics and anticoagulant utilization

	N	(%)	OAC users	(%)	*p* value
Overall	11,056		7238	(65.5)	
Age group					0.001
65–69	2302	(20.8)	1440	(62.6)	
70–74	2565	(23.2)	1667	(65.0)	
≥ 75	6189	(56.0)	4131	(66.7)	
Sex					0.005
Male	5751	(52.0)	3695	(64.2)	
Female	5305	(48.0)	3543	(66.8)	
Insurance type					0.425
NHI	10,215	(92.4)	6698	(65.6)	
MedAid/PVI	841	(7.6)	540	(64.2)	
CHF					< 0.001
No	5759	(52.1)	3679	(63.9)	
Yes	5297	(47.9)	3559	(67.2)	
Hypertension					< 0.001
No	1368	(12.4)	777	(56.8)	
Yes	9688	(87.6)	6461	(66.7)	
Diabetes mellitus					0.030
No	6771	(61.2)	4380	(64.7)	
Yes	4285	(38.8)	2858	(66.7)	
Prior stroke/TIA/TE					< 0.001
No	8798	(79.6)	5621	(63.9)	
Yes	2258	(20.4)	1617	(71.6)	
Vascular disease					< 0.001
No	10,260	(92.8)	6818	(66.5)	
Yes	796	(7.2)	420	(52.8)	
Anemia					< 0.001
No	9930	(89.8)	6599	(66.5)	
Yes	1126	(10.2)	639	(56.8)	
Severe renal disease					< 0.001
No	10,911	(98.7)	7183	(65.8)	
Yes	145	(1.3)	55	(37.9)	
Prior hemorrhage diagnosis					< 0.001
No	10,496	(94.9)	6929	(66.0)	
Yes	560	(5.1)	309	(55.2)	
Type of medical institution					< 0.001
Tertiary	4424	(40.0)	3221	(72.8)	
General	5291	(47.9)	3380	(63.9)	
Primary & others	1341	(12.1)	637	(47.5)	
Region					< 0.001
Capital	3112	(28.1)	2126	(68.3)	
Metropolitan	2944	(26.6)	1950	(66.2)	
Others	5000	(45.2)	3162	(63.2)	
Aspirin use					< 0.001
No	9326	(84.4)	6860	(73.6)	
Yes	1730	(15.6)	378	(21.9)	
AF type					< 0.001
Paroxysmal	4847	(43.8)	2951	(60.9)	
Persistent	1475	(13.3)	1084	(73.5)	
Permanent	1160	(10.5)	816	(70.3)	
Atrial flutter	46	(0.4)	24	(52.2)	
Others	3528	(31.9)	2363	(67.0)	

AF atrial fibrillation, *CHF* congestive heart failure, *MedAid* medical aid, *NHI* National Health Insurance, *PVI* Patriots & Veterans Insurance, *TE* thromboembolism, *TIA* transient ischemic attack

receiving aspirin than in those not receiving aspirin. The anticoagulant utilization rate was the highest for persistent AF, followed by permanent AF, paroxysmal AF, and AFL.

Predictors of anticoagulants utilization

Table 2 presents the results of the multiple logistic regression analysis. Anticoagulant use was higher in patients aged ≥ 75 years than in those aged 65–69 years. Among comorbidities, hypertension was the most influential factor (odds ratio [OR] = 1.644; confidence interval [CI] = 1.445–1.869). Aspirin use had a significantly low OR (OR = 0.097; CI = 0.085–0.110) of anticoagulant use. OAC use was approximately 1.5 times higher in patients with persistent or permanent AF than in those with paroxysmal AF.

Discussion

In this study, the anticoagulant underutilization rate was estimated to be 34.5%, which appeared to be better than that reported in previous studies. In a cross-sectional study using National Patients Sample data compiled by the HIRA in 2009, 64.0% of patients with AF and risk factors did not use OAC for one year [16]. In another study using APS data, it decreased annually from 68% in 2011 to 62.5% in 2014 [15]. In a study on the temporal trends of antithrombotic therapy for stroke prevention, OAC prescription showed a constant increase from 32.0% in 2008 to 46.0% in 2015 [17]. Since the method of defining underutilization in each study was different, it is difficult to directly compare the results of these studies, but the overall underutilization rate tended to decrease. However, it is important to note that one-third of the patients with NVAF at high risk of stroke do not receive OAC according to our study. Anticoagulant therapy is suboptimal for patients with AF globally [1, 11], and the anticoagulant therapy rate is relatively lower in patients with NVAF in Asia than in other regions worldwide [19, 20]. The data from GARFIELD-AF (Global Anticoagulant Registry in the FIELD-Atrial Fibrillation) revealed that

Table 2 Adjusted odds ratios and 95% confidence intervals from the multiple logistic regression analysis of anticoagulant utilization

Explanatory variables		Anticoagulant utilization		
		Adj. OR	95% CI	*p* value
Age group	65–69 (R)			
	70–74	1.167	1.023–1.332	0.022
	≥ 75	1.210	1.080–1.355	0.001
Sex	Male (R)			
	Female	1.061	0.971–1.160	0.192
CHF	No (R)			
	Yes	1.103	1.008–1.208	0.033
Hypertension	No (R)			
	Yes	1.644	1.445–1.869	< 0.001
Diabetes mellitus	No (R)			
	Yes	1.168	1.065–1.281	0.001
Prior stroke/TIA/TE	No (R)			
	Yes	1.444	1.289–1.619	< 0.001
Vascular disease	No(R)			
	Yes	0.597	0.507–0.704	< 0.001
Anemia	No(R)			
	Yes	0.648	0.560–0.751	< 0.001
Severe renal disease	No(R)			
	Yes	0.289	0.200–0.416	< 0.001
Prior hemorrhage diagnosis	No(R)			
	Yes	0.610	0.502–0.741	< 0.001
Type of medical institution	Tertiary (R)			
	General	0.624	0.563–0.691	< 0.001
	Primary & others	0.325	0.281–0.375	< 0.001
Region	Capital (R)			
	Metropolitan	1.006	0.889–1.139	0.921
	Others	1.021	0.910–1.145	0.721
Aspirin use	No (R)			
	Yes	0.097	0.085–0.110	< 0.001
AF type	Paroxysmal (R)			
	Persistent	1.593	1.381–1.841	< 0.001
	Permanent	1.520	1.304–1.776	< 0.001
	Atrial flutter	0.530	0.283–1.004	0.048
	Others	1.183	1.067–1.313	0.001
c statistic	0.742			
p value of Hosmer–Lemeshow test	0.384			

Adj. OR adjusted odds ratio, *AF* atrial fibrillation, *CHF* congestive heart failure, *CI* confidence interval, *R* reference, *TE* thromboembolism, *TIA* transient ischemic attack

anticoagulant treatment rate with vitamin K antagonist (VKA) was lower in newly diagnosed NVAF patients in Asia than in other regions (37.8% vs. 53.3%) [19]. GLORIA-AF (Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation) also reported that anticoagulant treatment was less in Asia, where 55.2% of NVAF patients received NOAC or VKA between November 2011 and December 2014 compared to patients in Europe (90.1%), or North America (78.3%) [20]. The benefits of anticoagulant therapy in patients with AF have been established regardless of ethnicity [21–24]; hence, anticoagulant therapy should be administered to all eligible patients.

The diversification of OAC options after the introduction of NOACs has contributed to the reduction in the anticoagulant underutilization rate. By analyzing the type of anticoagulant used, NOACs have surpassed warfarin as an OAC treatment choice. Until 2014, the percentage

of NOACs in OACs in AF patients was less than 10% in South Korea [15, 25], but increased significantly to 36.2% in 2015 and 60.8% in 2016 [25]. In another study, NOAC use was estimated to be 10.8% of OAC use in 2013, which increased to 48.3% in 2015 [17]. In our study, it further increased to 87.1%. This result is consistent with the findings of separate studies from other countries. In a study using the Danish nationwide registry, the pattern of initiating OAC treatment was 41% with NOAC in January 2012, but it increased to 76% in December 2015 [26]. Another study using the United Kingdom Clinical Practice Research Datalink showed similar results [27]. In patients with AF and VTE, new VKA use decreased by 31% between 2009 and 2015, while new NOAC use increased by 17-fold between 2012 and 2015, and 56.5% of all OAC prescriptions were NOACs in 2015 [27]. It seems a reasonable change considering that compared to warfarin, NOACs are less susceptible to interactions with food or other drugs and have the advantage of not requiring regular blood tests. In our study, the most used NOAC was rivaroxaban, consistent with that reported in a previous study in 2015 [17]. While the UK study showed the same trend as our study in 2015, apixaban was the most preferred NOAC in Denmark in the same year [26, 27].

When comparing the risk factors for anticoagulant underutilization with those of previous studies, it is remarkable that women no longer have higher underutilization rates than men [15–17]. This is in line with the findings from previous studies, in which the transition from warfarin to NOAC was faster in women [28]. It is presumed that women were less satisfied with warfarin therapy, and the improvement in treatment rate after the introduction of new drugs was more prominent in female patients than in male patients [28].

Anemia, severe renal disease, and prior hemorrhage are comorbidities that significantly increase the bleeding risk as a component of the ATRIA (anticoagulation and risk factors in AF) bleeding score along with age (> 75 years) and hypertension. Although current guidelines recommend that a high bleeding risk score cannot be a contraindication to anticoagulant therapy [7–9, 29], OAC is still avoided in these patients. Moreover, NOAC has reduced the bleeding risk in Asians [30, 31], and it is presumed that the fear of bleeding still has a significant effect on OAC utilization. Recognizing that the benefits outweigh the risks of anticoagulation even in patients with a high bleeding risk is important for appropriate anticoagulant therapy. Aspirin use is one of the most significant risk factors of anticoagulant underutilization. OAC underutilization for AF may be perpetuated by aspirin use, which remains a soft option for physicians based on a misunderstanding of the safety and efficacy of aspirin [32]. GLORIA-AF revealed that aspirin use was inversely associated with anticoagulant utilization [20]. Several studies have demonstrated that aspirin has no benefit for stroke prevention in patients with AF and increases the risk of bleeding [33–35]. Hence, aspirin has been excluded from the treatment options in recent guidelines [7, 9, 36, 37], but these changes have not been fully integrated in clinical practice. Aspirin should no longer be recognized as a soft option, and it is necessary to further encourage physicians to select a better antithrombotic option.

Based on the level of healthcare facilities, OAC use was the highest in tertiary hospitals, followed by general hospitals and primary medical institutions/others. This is consistent with the order of more active use of new treatments, which has been shown consistently in other studies [38]. Regarding AF types, the OAC utilization rate was significantly higher in patients with persistent and permanent AF than in those with paroxysmal AF and AFL. This seems to be related to the degree of stroke risk [39–41]. However, AF guidelines recommend OAC therapy for stroke prevention regardless of the AF type [7–10] since significant episodes of stroke occur even in patients with paroxysmal AF [42]. There was no significant difference depending on the region.

This study has some limitations. First, we used claims data, which were collected with the purpose of reimbursement and not for clinical or research purposes; therefore, information on diagnosis may be susceptible to upcoding by providers looking for a higher reimbursement rate [43]. Moreover, since the data did not include uninsured events, we could not obtain some information, such as over-the-counter aspirin use. Second, these claims data did not contain clinical data such as laboratory test results, disease severity, or patient-reported outcomes [44]. Therefore, we estimated the clinical status of patients using the provided disease codes ("Appendix"). Third, socioeconomic factors such as income, education, and health behaviors were not reflected. Finally, AF types are difficult to distinguish clearly, and the proportion classified as others is quite high (31.9%); therefore, the effect of AF type on OAC use may not be accurate.

Despite these limitations, this study is meaningful. It reports the use of anticoagulants in the recent time when OAC choices have become diverse and NOACs are widely used. In addition, in this study, we defined only those who were taking medication as of July 1, 2018, as OAC users for obtaining data closer to the actual use, unlike previous studies that used the conservative method of defining OAC users if OAC was used even once a year.

Conclusion

This study demonstrates that approximately one-third of patients who are recommended anticoagulation therapy do not take OAC, even though using NOACs has become more common. It should be widely recognized that aspirin cannot be an alternative to OAC, and anticoagulant therapy should be actively implemented.

Appendix: Disease and medication codes

Disease	
Atrial fibrillation	I48, I480–I484, I489
Paroxysmal atrial fibrillation	I480
Persistent atrial fibrillation	I481
Permanent atrial fibrillation	I482
Atrial flutter	I483–484
Atrial fibrillation and atrial flutter	I48, I489
Congestive heart failure	I50, I110, I130, I132
Hypertension	I10–13
Diabetes mellitus	E10–14
Prior stroke or transient ischemic attack or thromboembolism	G45, I26, I63-64, I676, I74, I80, I82
Vascular disease	I21–24, I70, I73
Anemia	D50–53, D55, D59–64
Severe renal disease	N184-185, T824, Y841, Z49, Z940, Z992
Renal disease	I12–13, N03–05, N10–12, N14–19, Z940, N184–185, T824, Y841, Z49, Z992
Previous hemorrhage	I60–62, I690–692, K2211, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K290, K625, K920–922
Valvular heart disease	I050, I052, I059, I080–081, I083, I089, I342, I349, T820, T826, Z952–954
Medication	
Dabigatran	613701AC, 613702AC
Rivaroxaban	511401AT, 511402AT, 511403AT, 511404AT
Apixaban	617001AT, 617002AT
Edoxaban	643601AT, 643602AT, 643603AT
Warfarin	249103AT, 249105AT
Aspirin	110701AT, 110702AT, 110801AT, 110802AT, 111001AC, 111001AT, 111002AT, 111003AC, 111003AT, 517900AC, 517900AT, 667500AC, 489700AC

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