Journal of the Formosan Medical Association (2016) xx, 1–11

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.jfma-online.com

ORIGINAL ARTICLE

Factors driving the use of warfarin and non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation

Mu-Mei Hu [a,b], Jui Wang [c], Kuo-Liong Chien [c,d], Chin-Ling Su [b], Shin-Yi Lin [b,e], Fe-Lin Lin Wu [a,b,e,*], Zhen-Fang Lin [a,b,e,*]

[a] *Graduate Institute of Clinical Pharmacy, College of Medicine, National Taiwan University, Taipei, Taiwan*
[b] *Department of Pharmacy, National Taiwan University Hospital, Taipei, Taiwan*
[c] *Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan*
[d] *Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan*
[e] *School of Pharmacy, College of Medicine, National Taiwan University, Taipei, Taiwan*

Received 17 March 2016; received in revised form 17 May 2016; accepted 19 May 2016

KEYWORDS
anticoagulants;
atrial fibrillation;
dabigatran;
warfarin

Background/purpose: In the past, warfarin was the drug of choice for stroke prevention in patients with atrial fibrillation (AF). Recently, non-vitamin K antagonist oral anticoagulants (NOACs) have been approved as an alternative to warfarin in nonvalvular AF. However, there is a limited amount of real-world data on how NOACs are currently being used in Taiwan. This study was conducted to investigate the factors driving the initiation of anticoagulants and the selection of different anticoagulants in patients with AF.

Methods: We used National Taiwan University Hospital's electronic database to identify all nonvalvular AF patients from January 1, 2007 to December 31, 2013. Multivariate logistic regression models were used to examine the factors driving the initiation of anticoagulants and the selection of different anticoagulants.

Results: Among AF patients, 66.4% of anticoagulants users used NOACs instead of warfarin after the era of NOACs. Patients with female sex, hypertension, ischemic heart disease, cancer, hepatic disease, renal disease, bleeding history, and aspirin use were less likely to be anticoagulant users but are more likely to be anticoagulant users with a history of stroke (odds ratio = 2.64; 95% confidence interval, 2.02–3.45). Older age, ischemic heart disease, and

Conflicts of interest: The authors have no conflicts of interest relevant to this article.

* Corresponding authors. Zhen-Fang Lin, School of Pharmacy and Graduate Institute of Clinical Pharmacy, College of Medicine, National Taiwan University, Room 206, 2F, Number 33, Linsen S. Road, Zhongzheng District, Taipei 10050, Taiwan. Fe-Lin Lin Wu, School of Pharmacy and Graduate Institute of Clinical Pharmacy, College of Medicine, National Taiwan University, 33 Linsen S. Road, Taipei 100, Taiwan.
E-mail addresses: flwu@ntu.edu.tw (F.-L.L. Wu), zflin@ntu.edu.tw (Z.-F. Lin).

http://dx.doi.org/10.1016/j.jfma.2016.05.007

aspirin use were the factors associated with NOACs usage, whereas hepatic disease showed the opposite results (odds ratio = 0.09; 95% confidence interval, 0.02—0.42).
Conclusion: Stroke history was associated with anticoagulant use, whereas comorbidities associated with increased risk of bleeding showed the opposite result. Patients with hepatic disease were less likely to use NOACs.

Introduction

Atrial fibrillation (AF) is a common arrhythmia encountered in clinical practice. Stroke is one of the complications of AF, which results in serious disability and increased economic burden for patients and their families. In the past, warfarin was the drug of choice for stroke prevention in AF patients, especially for those at higher risk.[1] However, reports showed underuse of warfarin.[2,3] Nearly 28% of AF patients received warfarin in the Taiwan Stroke Registry from 2006 to 2008.[4] Only 24.7% of AF patients received appropriate antithrombotic therapy according to treatment guideline in a study performed using the National Health Insurance Research Database (NHIRD) between 2003 and 2004.[5]

Non-vitamin K antagonist oral anticoagulants (NOACs), including dabigatran, rivaroxaban, apixaban, and edoxaban, have shown more encouraging efficacy and safety profiles compared to warfarin.[6—10] Current treatment guidelines suggest NOACs as alternatives to warfarin in nonvalvular AF.[11,12] Some reports from Denmark have explored the use of NOACs and factors associated with the use of NOACs after they were approved for release on the market.[13,14] Since 2012, NOACs have been available in Taiwan. So far, there is limited real-world data on how NOACs are currently being used as well as factors driving the initiation and selection of anticoagulants. The objective of our study is to investigate factors driving the initiation of anticoagulants (anticoagulant vs. no anticoagulant) and the selection of different anticoagulants (warfarin or NOACs) in Taiwan.

Methods

Data source

We used National Taiwan University Hospital's (NTUH) electronic database from 2006 to 2013 as our data source. NTUH is a 2500-bed tertiary medical center that serves 2000 inpatients and 8000 outpatients daily. The database provides information from outpatient, inpatient, and emergency departments with the disease diagnosis according to International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes as well as surgery and procedure records for the patients. All prescription records are available from the pharmacy department. Using specified identification code for each patient, all information can be linked together. Our study was approved by the institutional review board of the NTUH.

Study design

We first identified newly diagnosed AF patients from 2007 to 2013. Newly diagnosed was defined as no AF disease codes (ICD-9-CM code 427.31) present in the database from outpatient, inpatient, or emergency department in 2006. Patients with at least three AF disease codes from January 1, 2007 to December 31, 2013 were recruited into study. Individuals with no age record or younger than 20 years were excluded. Patients with valvular AF (history of rheumatic heart disease, or had undergone valve repair or replacement), history of pulmonary embolism or deep vein thrombosis, or had undergone hip or knee replacement within 1 year prior to study entry were excluded. Anticoagulant users were grouped according to the first anticoagulant prescription record after AF was first diagnosed. Dabigatran (110 mg; available since February 1, 2013) and rivaroxaban (20 mg; available since November 1, 2013) were the two available NOACs during the study period. For patients with no anticoagulant treatment throughout study, the date when AF was first diagnosed served as their index date. The date of the first anticoagulant prescription was defined as the index date for anticoagulant users.

Definition for variables

Records related to comorbidities, surgeries, and concomitant medications were collected within 12 months prior to the index date. Comorbidities were defined as ICD-9-CM codes present in the hospital database within 1 year prior to the index date. The ICD-9-CM codes used in our study are shown in Appendix 1. Information related to valve repair, valve replacement, and hip or knee replacement were defined using the codes for surgery and physician orders provided by the Information Technology Center from NTUH. The codes are listed in Appendix 2. Generic names for concomitant medications used in the study are given in Appendix 3. The $CHADS_2$ score indicates congestive heart failure, hypertension, age $\geq$75 years, diabetes mellitus, prior stroke or TIA (transient ischemic attack) or TE (thromboembolism) score; CHA_2DS_2-VASc score for congestive heart failure, hypertension, age $\geq$75 years, diabetes mellitus, prior stroke or TIA or TE, vascular disease, age 65—74 years, sex category point score systems; HAS-BLED score for hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR (international normalized ratio), age older than 65 years, concomitant use of drugs or alcohol. Calculations for the scoring systems mentioned above were made using

Please cite this article in press as: Hu M-M, et al., Factors driving the use of warfarin and non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation, Journal of the Formosan Medical Association (2016), http://dx.doi.org/10.1016/j.jfma.2016.05.007

comorbidities and concomitant medications in Appendices 1 and 3. We also collected INR values and alcohol use from social history. Labile INR and alcohol use were not calculated in HAS-BLED score because some patients had missing data. Patients who had their first anticoagulant prescription in 2013 were analyzed to provide information on warfarin versus NOAC use after the introduction of NOACs to NTUH. Data were presented using total patient number of first anticoagulant initiation and the percentage of warfarin and NOAC use in each month.

Statistical analysis

To compare baseline characteristics between groups, *t* test or analysis of variance (ANOVA) was used for continuous variables, whereas chi-square test was used for categorical variables. Two multivariate logistic regression models were used to examine the factors driving the initiation of anticoagulants and the selection of different anticoagulants. No anticoagulant treatment and warfarin usage served as a reference group in each model where factors driving the

Table 1 Patient demographics.

Variables	Total patient (n = 3662)	No anticoagulant treatment (n = 2447)	Anticoagulant treatment (n = 1215)	p	Warfarin (n = 928)	NOACs (n = 287)	p
Age, mean (SD)	69.9 (12.8)	70.3 (13.0)	69.1 (12.3)	0.01	67.1 (12.4)	75.7 (9.5)	<0.01
<65 y, *n* (%)	1217 (33.2)	804 (32.9)	413 (34.0)	<0.01	379 (40.8)	34 (11.9)	<0.01
65–74 y, *n* (%)	1031 (28.2)	655 (26.8)	376 (31.0)		285 (30.7)	91 (31.7)	
≥75 y, *n* (%)	1414 (38.6)	988 (40.3)	426 (35.0)		264 (28.5)	162 (56.5)	
$CHADS_2$ score, mean (SD)	1.4 (1.2)	1.4 (1.1)	1.5 (1.2)	0.19	1.4 (1.2)	1.8 (1.1)	<0.01
CHA_2DS_2-VASc score, mean (SD)	2.8 (1.7)	2.8 (1.6)	2.8 (1.7)	0.60	2.6 (1.7)	3.5 (1.5)	<0.01
HAS-BLED score, mean (SD)	2.0 (1.1)	2.0 (1.1)	1.9 (1.1)	0.03	1.8 (1.2)	2.3 (1.0)	<0.01
Female, *n* (%)	1667 (45.5)	1147 (46.9)	520 (42.8)	0.02	386 (41.6)	134 (46.7)	0.13
Comorbidities, *n* (%)							
Hypertension	1908 (52.1)	1309 (53.5)	599 (49.3)	0.02	435 (46.9)	164 (57.1)	<0.01
Heart failure	661 (18.1)	425 (17.4)	236 (19.4)	0.13	178 (19.2)	58 (20.2)	0.70
Ischemic heart disease	1002 (27.4)	695 (28.4)	307 (25.3)	0.04	207 (22.3)	100 (34.8)	<0.01
Dyslipidemia	709 (19.4)	461 (18.8)	248 (20.4)	0.26	176 (19.0)	72 (25.1)	0.02
Diabetes	762 (20.8)	509 (20.8)	253 (20.8)	0.99	172 (18.5)	81 (28.2)	<0.01
Hyperthyroidism	114 (3.1)	75 (3.1)	39 (3.2)	0.81	33 (3.6)	6 (2.1)	0.22
Sick sinus syndrome	174 (4.8)	117 (4.8)	57 (4.7)	0.90	37 (4.0)	20 (7.0)	0.04
Hypertrophic cardiomyopathy	19 (0.5)	9 (0.4)	10 (0.8)	0.07	5 (0.5)	5 (1.7)	0.06
Peripheral vascular disease	59 (1.6)	42 (1.7)	17 (1.4)	0.47	7 (0.8)	10 (3.5)	<0.01
Stroke/TIA/TE	266 (7.3)	126 (5.2)	140 (11.5)	<0.01	112 (12.1)	28 (9.8)	0.28
Cancer	343 (9.4)	255 (10.4)	88 (7.2)	<0.01	54 (5.8)	34 (11.9)	<0.01
Hepatic disease	140 (3.8)	108 (4.4)	32 (2.6)	0.01	27 (2.9)	5 (1.7)	0.28
Renal disease	242 (6.6)	196 (8.0)	46 (3.8)	<0.01	41 (4.4)	5 (1.7)	0.04
Peptic ulcer disease	177 (4.8)	113 (4.6)	64 (5.3)	0.39	41 (4.4)	23 (8.0)	0.02
Thrombocytopenia	9 (0.3)	6 (0.3)	3 (0.3)	0.99	1 (0.1)	2 (0.7)	0.14
Bleeding history	256 (7.0)	188 (7.7)	68 (5.6)	0.02	45 (4.9)	23 (8.0)	0.04
Dementia	89 (2.4)	62 (2.5)	27 (2.2)	0.56	13 (1.4)	14 (4.9)	<0.01
Psychiatric disease	4 (0.1)	4 (0.2)	0 (0.0)	0.31	0 (0.0)	0 (0.0)	NA
Concomitant medications, *n* (%)							
Antihypertensive agents	3109 (84.9)	2027 (82.8)	1082 (89.1)	<0.01	813 (87.6)	269 (93.7)	<0.01
Antidyslipidemic agents	677 (18.5)	424 (17.3)	253 (20.8)	0.01	185 (19.9)	68 (23.7)	0.17
Antidiabetic agents	697 (19.0)	445 (18.2)	252 (20.7)	0.06	182 (19.6)	70 (24.4)	0.08
Medications associated with increased bleeding tendency	1463 (40.0)	972 (39.7)	491 (40.4)	0.69	370 (39.9)	121 (42.2)	0.49
Medications associated with decreased bleeding tendency	865 (23.6)	548 (22.4)	317 (26.1)	0.01	241 (26.0)	76 (26.5)	0.86
Aspirin	1629 (44.5)	1100 (45.0)	529 (43.5)	0.42	377 (40.6)	152 (53.0)	<0.01
Clopidogrel	368 (10.1)	249 (10.2)	119 (9.8)	0.72	86 (9.3)	33 (11.5)	0.27

$CHADS_2$ score = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or TIA (transient ischemic attack) or TE (thromboembolism) score; CHA_2DS_2-VASc score = congestive heart failure, hypertension, age ≥75 years (doubled), diabetes mellitus, prior stroke or TIA or TE (doubled), vascular disease, age 65–74 years, sex category point score systems; HAS-BLED score = hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR (international normalized ratio), elderly, drugs/alcohol (concomitant use); NA = not available; NOACs = non-vitamin K antagonist oral anticoagulants; SD = standard deviation.

Please cite this article in press as: Hu M-M, et al., Factors driving the use of warfarin and non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation, Journal of the Formosan Medical Association (2016), http://dx.doi.org/10.1016/j.jfma.2016.05.007

initiation and selection of anticoagulants were explored. Factors were reported as odds ratio (OR) with 95% confidence intervals (CIs). Cochran–Armitage test was used to examine the trend for warfarin and dabigatran users over 2013. A p value <0.05 was considered statistically significant. We performed all the analyses using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Study population

There were 3662 nonvalvular AF patients recruited in the study. Patient demographics are shown in Table 1. The average age was 69 years; 38.6% of patients were $\geq$75 years old and 45.5% were female. In the study population, hypertension was the most common comorbidity (52.1%), and 27.4% had ischemic heart disease, 20.8% had diabetes, and 19.2% had dyslipidemia. Of the 3662 nonvalvular AF patients, 33.2% were anticoagulant users whereas 53.8% were anticoagulant users after the era of NOACs. Among anticoagulant users, 66.4% and 27.2% were on NOACs and warfarin, respectively, after the era of NOACs (Figure 1). The average $CHADS_2$ score [standard deviation (SD)], CHA_2DS_2-VASc score, and HAS-BLED score were 1.4 (SD = 1.2), 2.8 (1.7), and 2.0 (1.1), respectively. Patients with no anticoagulant treatment generally were older (40.3% were older than 75 years) compared to anticoagulant users. Patients with first prescription of NOACs were older (56.5% were older than 75 years) compared to warfarin (40.8% were younger than 65 years). There were similar CHA_2DS_2-VASc score and HAS-BLED score between the no anticoagulant treatment group and the anticoagulant treatment group. Higher CHA_2DS_2-VASc score and HAS-BLED score were found in the NOACs group compared to the warfarin group (mean CHA_2DS_2-VASc score 3.5 in NOACs vs. 2.6 in warfarin, $p < 0.01$; mean HAS-BLED score 2.3 in NOACs vs. 1.8 in warfarin, $p < 0.01$) (Figure 2). In comparison, there were more patients with hypertension

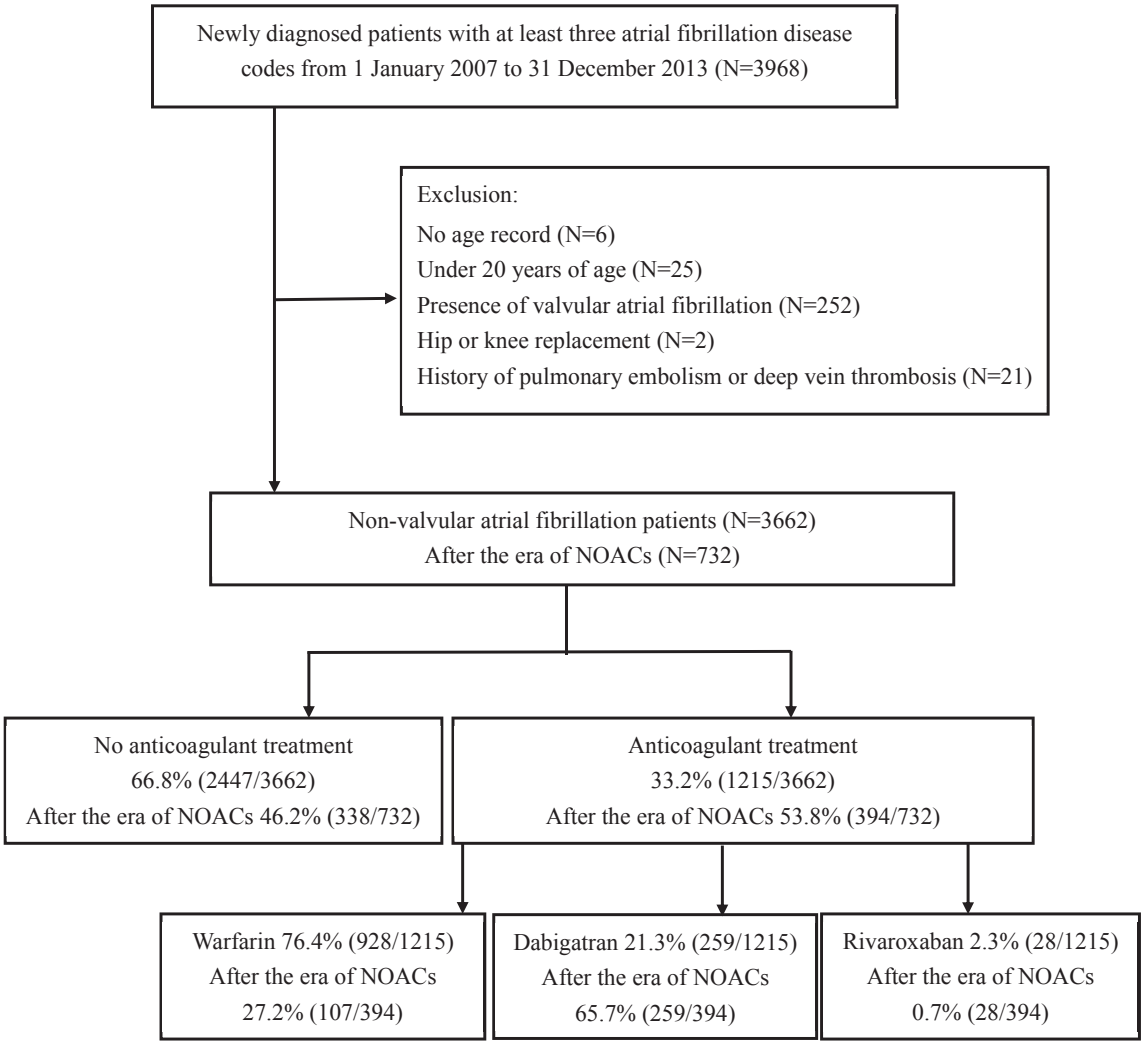
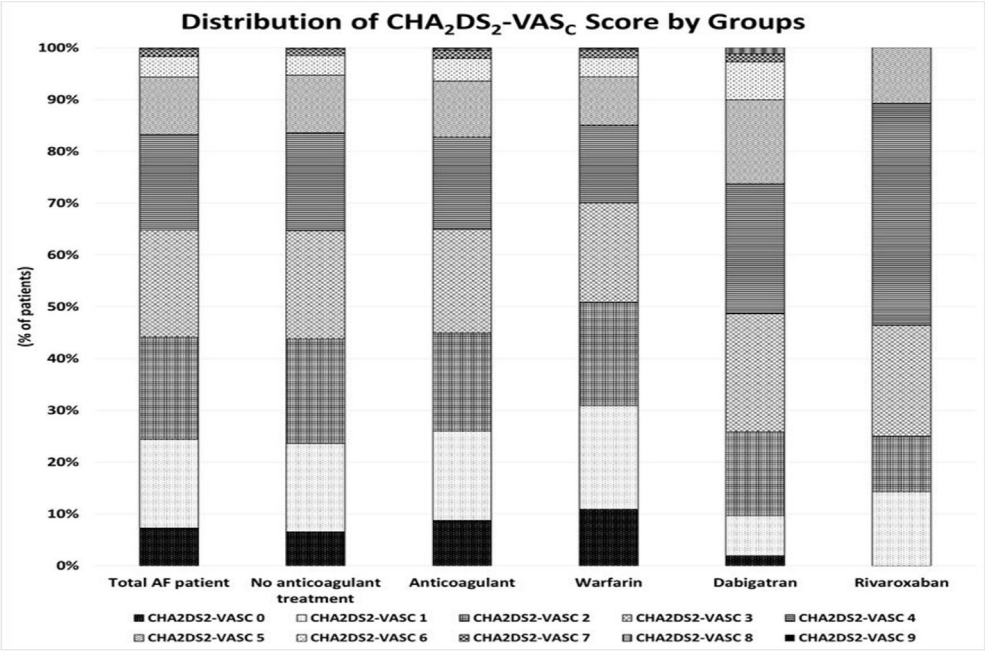


Figure 1 Patient enrollment flowchart for the study.

Please cite this article in press as: Hu M-M, et al., Factors driving the use of warfarin and non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation, Journal of the Formosan Medical Association (2016), http://dx.doi.org/10.1016/j.jfma.2016.05.007

A. CHA_2DS_2-VASc score



B. HAS-BLED score

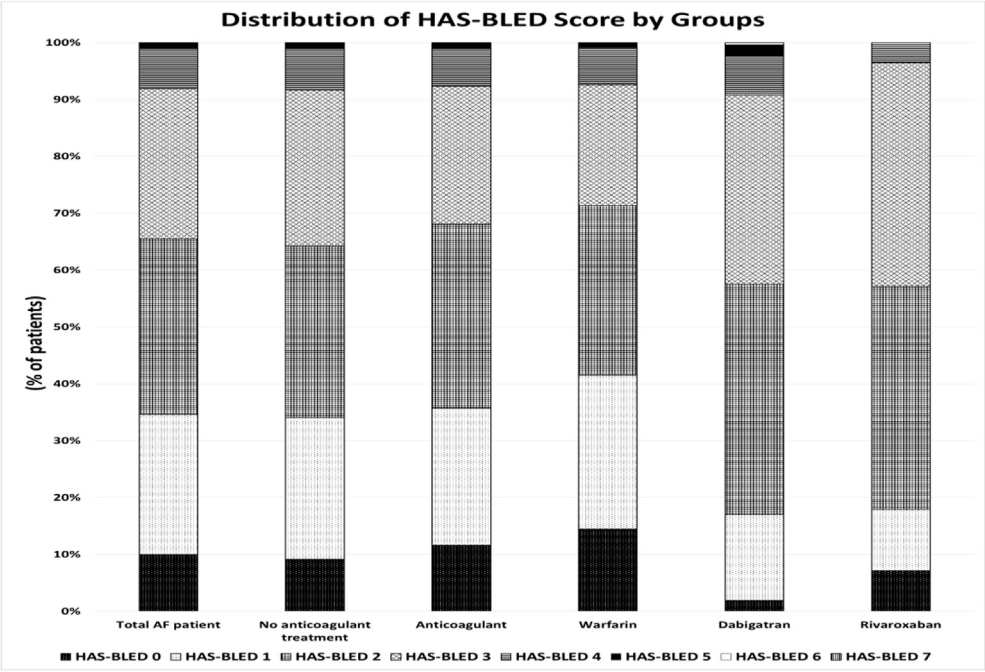


Figure 2 Distribution of CHA2DS2-VASc score and HAS-BLED score in atrial fibrillation patients with different anticoagulants. (A) Distribution of CHA2DS2-VASc score. (B) Distribution of HAS-BLED score. CHA2DS2-VASc = for congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or TIA or TE, vascular disease, age 65—74 years, sex category (i.e., female sex) point score systems; HAS-BLED = hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly (age, older than 65 years), concomitant use of drugs or alcohol.

in the no anticoagulant treatment group than in the anticoagulant treatment group (53.5% vs. 49.3%, $p = 0.02$). There were more patients with ischemic heart disease in the no anticoagulant treatment group than in the anticoagulant treatment group (28.4% vs. 25.3%, $p = 0.04$). The percentage of patients with stroke/TE/TIA history in the anticoagulant treatment group was 2.2-fold higher than that in the no anticoagulant treatment group (11.5% vs. 5.2%, $p < 0.01$). On the contrary, there were more patients with a history of cancer, hepatic disease, renal disease,

Please cite this article in press as: Hu M-M, et al., Factors driving the use of warfarin and non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation, Journal of the Formosan Medical Association (2016), http://dx.doi.org/10.1016/j.jfma.2016.05.007

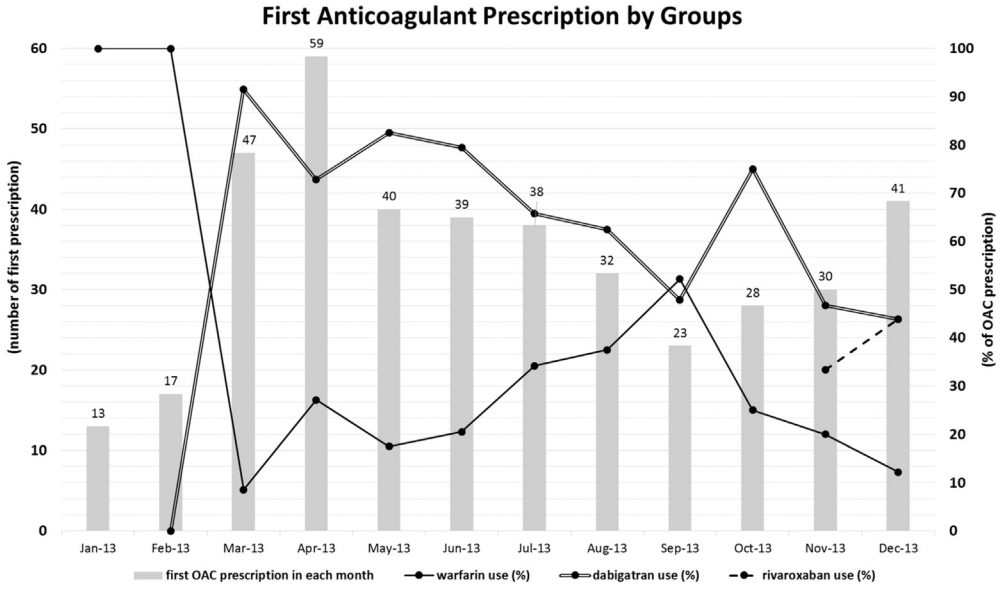


Figure 3 First anticoagulant prescription trend in 2013. Cochran—Armitage test for trends of warfarin versus dabigatran use: $p < 0.01$. OAC = oral anticoagulation.

and bleeding events in the no anticoagulant treatment group (cancer: 10.4% vs. 7.2%, $p < 0.01$; hepatic disease: 4.4% vs. 2.6%, $p = 0.01$; renal disease: 8.0% vs. 3.8%, $p < 0.01$; bleeding history: 7.7% vs. 5.6%, $p < 0.02$). There were more patients with hypertension, ischemic heart disease, diabetes, and peripheral vascular disease in the NOACs group than in the warfarin group ($p < 0.01$ for all comorbidities listed above). A higher percentage of hepatic and renal diseases (hepatic disease: 2.9% vs. 1.7%; renal disease: 4.4% vs. 1.7%) and a lower percentage of bleeding history (4.9% vs. 8.0%) were noted in the warfarin group compared to the NOACs group. There was more frequent aspirin and clopidogrel use in the no anticoagulant treatment and NOACs group than in the anticoagulant and warfarin group.

First anticoagulant prescription trend in 2013

Trends for first anticoagulant prescription after February 1, 2013 showed increased dabigatran use (Figure 3). The percentage of dabigatran as first anticoagulant use in each month reached its peak 1 month after the introduction of dabigatran in the NTUH (91.5% in March 2013), followed by a slow decline until December 2013 (43.9%). The percentage of warfarin prescription kept trending down from 100% in February 2013 to 12.2% in December 2013. The decrease in warfarin use was mainly reflected by increased dabigatran use ($p < 0.01$ for trends of warfarin vs. dabigatran use).

Factors driving the initiation of anticoagulants

Adjustment for age, sex (male as reference group), comorbidities, concomitant medications, aspirin and clopidogrel use was made in the multivariate logistic regression models. The result for factors driving the initiation of anticoagulant therapy is listed in Table 2. Female sex, hypertension, ischemic heart disease, cancer, hepatic disease, renal disease, bleeding history, and aspirin use were the negative predictors for anticoagulant usage. Among these predictors, hepatic disease (OR = 0.57; 95% CI, 0.38—0.86) and renal disease (OR = 0.43; 95% CI, 0.31—0.60) showed stronger negative association than others. Stroke/TE/TIA history, use of antihypertensive agents, use of antidiabetic agents, and medications associated with decreased bleeding tendency were positive predictors for anticoagulant use. Stroke/TE/TIA history was the strongest positive predictor (OR = 2.64; 95% CI, 2.02—3.45). After the era of NOACs, renal disease, bleeding history, and clopidogrel use were the negative predictors for anticoagulant use. Older age, peptic ulcer disease, and antihypertensive agents use were positive predictors for anticoagulant use.

Factors driving the selection of NOACs versus warfarin

After adjustment, predictors for the selection of NOACs versus warfarin are listed in Table 3. After the era of NOACs, older age (OR = 1.07; 95% CI, 1.04—1.10), ischemic heart disease (OR = 2.44; 95% CI, 1.21—4.92), antihypertensive agents use (OR = 2.76; 95% CI, 1.19—6.44), and aspirin use (OR = 1.93; 95% CI, 1.11—3.36) were the positive predictors associated with NOACs use. Hepatic disease (OR = 0.09; 95% CI, 0.02—0.42) was the positive predictor associated with warfarin usage.

Discussion

There were several major findings in our study. In factors driving the initiation of anticoagulant therapy, we found

Please cite this article in press as: Hu M-M, et al., Factors driving the use of warfarin and non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation, Journal of the Formosan Medical Association (2016), http://dx.doi.org/10.1016/j.jfma.2016.05.007

Table 2 Factors driving the initiation of anticoagulants.

Variables	Odds ratio (95% CI)	After the era of NOACs Odds ratio (95% CI)
Age	0.99 (0.98–1.00)	1.02 (1.00–1.03)*
Sex (female)	0.81 (0.70–0.94)*	0.84 (0.61–1.17)
Hypertension	0.82 (0.70–0.96)*	1.09 (0.77–1.53)
Heart failure	1.14 (0.95–1.37)	1.21 (0.81–1.82)
Ischemic heart disease	0.83 (0.69–0.99)*	1.05 (0.71–1.56)
Dyslipidemia	1.09 (0.87–1.37)	1.08 (0.67–1.76)
Diabetes	0.83 (0.63–1.09)	1.01 (0.57–1.82)
Hypertrophic cardiomyopathy	2.07 (0.82–5.22)	7.35 (0.78–69.51)
Hyperthyroidism	0.98 (0.65–1.48)	1.01 (0.41–2.49)
Peripheral vascular disease	0.78 (0.43–1.41)	0.54 (0.19–1.50)
Sick sinus syndrome	1.13 (0.81–1.58)	0.71 (0.37–1.36)
Cancer	0.61 (0.47–0.80)*	0.68 (0.40–1.14)
Hepatic disease	0.57 (0.38–0.86)*	0.54 (0.22–1.34)
Renal disease	0.43 (0.31–0.60)*	0.19 (0.09–0.41)*
Peptic ulcer disease	1.22 (0.87–1.71)	3.16 (1.36–7.34)*
Thrombocytopenia	1.06 (0.26–4.38)	1.40 (0.22–9.01)
Bleeding history	0.67 (0.49–0.92)*	0.54 (0.30–0.95)*
Dementia	0.83 (0.51–1.34)	1.86 (0.66–5.22)
Psychiatric disease	NA (NA)	NA (NA)
Stroke/TIA/TE	2.64 (2.02–3.45)*	1.64 (0.91–2.95)
Antihypertensive agents usage	1.94 (1.55–2.44)*	2.27 (1.41–3.64)*
Antidyslipidemic agents usage	1.19 (0.94–1.50)	1.27 (0.75–2.15)
Antidiabetic agents usage	1.37 (1.03–1.82)*	1.06 (0.57–1.97)
Medications with increased bleeding tendency	1.02 (0.86–1.21)	1.05 (0.72–1.54)
Medications with decreased bleeding tendency	1.25 (1.03–1.50)*	1.11 (0.75–1.64)
Aspirin usage	0.82 (0.70–0.95)*	1.35 (0.96–1.89)
Clopidogrel usage	0.89 (0.68–1.17)	0.54 (0.30–0.99)*

Medications associated with increased bleeding tendency, indicates anticancer agents with bleeding risk, anticoagulants except for warfarin and NOACs, antiplatelets, NSAID, fibrinolytic agents, steroids, ginkgo, pentoxifylline, piracetam. Medications associated with decreased bleeding tendency, indicates coagulation factors, tranexamic acid, H_2 blocker, proton pump inhibitors, vitamin K.
* Statistically significant.
CI = confidence interval; NA = not available; NOACs = non-vitamin K antagonist oral anticoagulants; NSAID = nonsteroidal anti-inflammatory drug; TE = thromboembolism; TIA = transient ischemic attack.

that stroke/TE/TIA history was strongly associated with anticoagulant use. The result can be supported by the recommendation of using these agents as secondary prevention for stroke in current treatment guidelines.[11,12] However, up to 5.2% of patients with stroke/TE/TIA history were found in the no anticoagulant treatment group. Judgment for benefit (stroke prevention) and risk (bleeding) prior to the initiation of anticoagulant therapy is the key. In our study, there was a comparable stroke risk between the anticoagulant treatment group versus the no anticoagulant treatment group according to $CHADS_2$ score and CHA_2DS_2-VASc score, whereas a higher HAS-BLED score was noted in the no anticoagulant treatment group, which showed bleeding risk as a major concern prior to initiating anticoagulants. For AF patients with acute coronary syndrome, dual antiplatelet therapy plus anticoagulant treatment may result in increased bleeding risk. The combination of these agents still remains to be a dilemma in clinical practice.[15] In our study, comorbidities related to increase bleeding risk were the negative predictors for anticoagulant usage. This was not only illustrated in the patient demographics between the two groups but is also consistent with the findings of Lin et al.[5]

As for the factors driving the selection of NOACs versus warfarin, we found that more physicians were willing to prescribe NOACs for patients as first anticoagulant prescription. Generally, increased uptake of dabigatran and decreased warfarin prescription were observed. However, there were fluctuations on the curve for warfarin and dabigatran prescription. This may be related to the patient characteristics each month, patient preference, side effect profile, and physicians' experience with the medication. Moreover, we found that older age, ischemic heart disease, antihypertensive agents use, and aspirin use were the positive predictors associated with NOACs use, whereas hepatic disease was a positive predictor associated with warfarin use after the era of NOACs. Of note, majority (98.9%) of NOACs users were under the coverage of the NHI program, and 90% were dabigatran users during the study period. Adherence with the NHI prescribing recommendations for dabigatran in Taiwan is cited as the reason why older age and ischemic heart disease were found as positive

Please cite this article in press as: Hu M-M, et al., Factors driving the use of warfarin and non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation, Journal of the Formosan Medical Association (2016), http://dx.doi.org/10.1016/j.jfma.2016.05.007

Table 3 Factors driving the selection of NOACs versus warfarin.

Variables	After the era of NOACs Odds ratio (95% CI)
Age	1.07 (1.04–1.10)*
Sex (female)	1.09 (0.63–1.87)
Hypertension	0.79 (0.44–1.42)
Heart failure	0.78 (0.41–1.49)
Ischemic heart disease	2.44 (1.21–4.92)*
Dyslipidemia	0.63 (0.29–1.37)
Diabetes	1.45 (0.51–4.13)
Hypertrophic cardiomyopathy	1.35 (0.16–11.72)
Hyperthyroidism	0.54 (0.13–2.20)
Peripheral vascular disease	NA (NA)
Sick sinus syndrome	2.09 (0.52–8.39)
Cancer	2.46 (0.86–7.02)
Hepatic disease	0.09 (0.02–0.42)*
Renal disease	0.30 (0.07–1.29)
Peptic ulcer disease	4.26 (0.90–20.10)
Thrombocytopenia	0.60 (0.04–8.57)
Bleeding history	0.78 (0.28–2.21)
Dementia	2.07 (0.40–10.78)
Psychiatric disease	NA (NA)
Stroke/TIA/TE	0.58 (0.25–1.37)
Antihypertensive agents usage	2.76 (1.19–6.44)*
Antidyslipidemic agents usage	1.08 (0.47–2.49)
Antidiabetic agents usage	0.68 (0.24–1.94)
Medications with increased bleeding tendency	1.09 (0.59–2.03)
Medications with decreased bleeding tendency	0.59 (0.31–1.11)
Aspirin usage	1.93 (1.11–3.36)*
Clopidogrel usage	0.76 (0.27–2.16)

Medications associated with increased bleeding tendency, indicates anticancer agents with bleeding risk, anticoagulants except for warfarin and NOACs, antiplatelets, NSAID, fibrinolytic agents, steroids, ginkgo, pentoxifylline, piracetam. Medications associated with decreased bleeding tendency, indicates coagulation factors, tranexamic acid, H_2 blocker, proton pump inhibitors, vitamin K.

* Statistically significant.

CI = confidence interval; NA = not available; NOACs = non-vitamin K antagonist oral anticoagulants; NSAID = nonsteroidal anti-inflammatory drug; TE = thromboembolism; TIA = transient ischemic attack.

predictors and hepatic disease as negative predictor of NOACs use after the era of NOACs. Aspirin use was a positive predictor for NOACs usage. This may be explained by the higher percentage of patients with ischemic heart disease in the NOACs group. However, concomitant use of aspirin and anticoagulant (regardless of whether warfarin or NOAC was used) leads to higher bleeding risk for patients, and, to our knowledge, there is no sufficient evidence guiding the combination use of NOACs and antiplatelet agents so far. Our finding requires further confirmation in future studies. Although NOACs are known for less food–drug interactions and do not require frequent blood testing, there is no sufficient evidence supporting the use of NOACs in patients with renal dysfunction and hepatic dysfunction so far. When it comes to therapeutic drug monitoring for warfarin, the INR is a good response marker for effectiveness and safety. More safety information regarding the use for NOACs should be provided in future studies.

To our knowledge, this is the first study in Taiwan to explore the factors driving the initiation and selection of anticoagulants. However, there are several limitations in our study. First, our results were obtained from a single medical center experience. However, it should be noted that the latest NHI database was not available during the time when we performed the study. Up to 98.9% of NOACs users were under the coverage of the NHI program, making our results more generalizable to the whole Taiwanese population. Second, the recruitment of patients was based on ICD-9-CM codes for AF owing to the lack of electrocardiogram results. We used at least three AF disease codes present in the electronic database as inclusion criteria, which is a stricter requirement compared with previous AF studies performed using the NHIRD.[5,16,17] Finally, other factors driving the initiation of warfarin and NOACs, including patient preference and adherence, were not available in our study. This type of information requires other study designs (e.g., chart review and questionnaire) to provide further results.

In our study, we have shown the real-world practice of anticoagulants and NOACs usage in patients with AF and factors driving the initiation of anticoagulants/selection of NOACs versus warfarin. These real-world data are a useful tool to monitor the adherence to the guideline-recommended anticoagulants and NOACs usage in patients with AF, and further strategies to improve the clinical practice can be implemented according to these results.

Conclusion

Our study provides the factors driving the initiation of anticoagulant treatment and the selection of different anticoagulants in NTUH. Among the patients who initiated anticoagulant treatment, 66.4% used NOACs instead of warfarin after the era of NOACs. Stroke history was associated with anticoagulant use, whereas comorbidities were associated with increased bleeding risk, showing opposite results. Patients with hepatic diseases were less likely to use NOACs. During the study period, the prescription rate of NOACs increased, and in warfarin users we found the opposite trend.

Acknowledgments

Z.F. Lin and M.M. Hu designed the research. C.L. Su, Z.F. Lin, and F.L. Lin Wu contributed to the acquisition of data. M.M. Hu and J. Wang analyzed the data. M.M. Hu and Z.F. Lin contributed to drafting the manuscript. F.L. Lin Wu, Z.F. Lin, S.Y. Lin, and K.L. Chien contributed to the clinical interpretation. All authors read and approved the content of the manuscript.

Appendix 1. ICD-9-CM codes used for defining comorbidities.

Comorbidities	ICD-9-CM code
Atrial fibrillation	427.31
Hypertension	401.xx, 402.xx, 403.xx, 404.xx, 405.xx
Heart failure	428.xx
Ischemic heart disease	410.xx, 411.xx, 412.xx, 413.xx, 414.xx
Dyslipidemia	272.xx
Diabetes	250.xx
Hyperthyroidism	242.xx
Sick sinus syndrome	427.81
Hypertrophic cardiomyopathy	425.1x
Peripheral vascular disease	443.xx
Ischemic stroke/	Ischemic stroke: 433.xx, 434.xx
Transient ischemic attack (TIA)/	TIA: 435.xx
Thromboembolism (TE)	TE: 453.xx, 415.xx
Cancer	140.xx～208.xx
Hepatic disease	570.xx～573.xx
Renal disease	580.xx～589.xx
Peptic ulcer disease	531.xx～534.xx
Thrombocytopenia	287.5
Rheumatic heart disease	393.xx～398.xx
Bleeding history	Definite bleeding: 531.0x, 531.2x, 531.4x, 531.6x, 532.0x, 532.2x, 532.4x, 532.6x, 533.0x, 533.2x, 533.4x, 533.6x, 534.0x, 534.2x, 534.4x, 534.6x, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 537.83, 456.0, 456.20, 530.7, 530.82, 578.0, 455.2, 455.5, 455.8, 562.02, 562.03, 562.12, 562.13, 568.81, 569.3, 569.85, 578.1, 578.9, 593.81, 599.7, 623.8, 626.2, 626.6, 430, 431, 432, 432.0, 432.1, 432.9, 852.0, 852.2, 852.4, 853.0, 423.0, 459.0, 568.81, 719.1x, 784.7, 784.8, 786.3 Critical site bleeding: 430, 431, 432, 852.0, 852.2, 852.4, 853.0, 336.1, 363.6, 372.72, 376.32, 377.42, 379.23, 719.1, 729.92, 729.97, 423.0, 593.81, 772.5, 866.01, 866.02, 866.11, 866.12
Dementia	290.xx
Psychiatric disease	295.xx

Note. The ICD-9-CM codes for bleeding history in our study were adapted from "An automated database definition for serious bleeding due to oral anticoagulant use," by A.W. Cunningham, C.M. Stein, C.P. Chung, J.R. Daugherty, W.E. Smalley, W.A. Ray, 2011, *Pharmacoepidemiol Drug Saf*, *20*, p. 560–66. Copyright 2016 by John Wiley and Sons. Adapted with permission.
ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

Appendix 2. Codes used for defining surgeries.

	Codes for surgery orders	Codes for physician orders				
Knee replacement	64164B00					
Hip replacement	64162B00					
Valve repair		68015B00	68029BZS	68029B0S		
		20360207	69033B00	20360204		
		20360206	68029B00			
Valve replacement	68016A00	20360144	20360150	68017B00	20360130	20360300
		20360143	20360142	20360148	20360131	20360111
		20360139	20360113	68016B00	20360141	20360304
		20360146	20360112	20360303	20360147	20360302
		20360110	20360114	68018B00	20360149	

Please cite this article in press as: Hu M-M, et al., Factors driving the use of warfarin and non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation, Journal of the Formosan Medical Association (2016), http://dx.doi.org/10.1016/j.jfma.2016.05.007

Appendix 3. Generic names for concomitant medications.

Medication	Generic names			
Antihypertensive agents				
ACEI	Captopril	Lisinopril	Benazepril	Fosinopril
	Enalapril	Ramipril	Cilazapril	Imidapril
ARB	Losartan	Irbesartan	Telmisartan	Azilsartan
	Valsartan	Candesartan	Olmesartan	
Beta blocker	Metoprolol	Propranolol	Bisoprolol	Acebutolol
	Atenolol	Nadolol	Sotalol	Betaxolol
	Esmolol	Carvedilol	Carteolol	Labetalol
DHP-CCB	Amlodipine	Isradipine	Nifedipine	Barnidipine
	Felodipine	Nicardipine	Nimodipine	Lercanidipine
Non-DHP-CCB	Diltiazem	Verapamil		
Diuretics	Acetazolamide	Indapamide	Bumetanide	Eplerenone
	Trichlormethiazide	Furosemide	Spironolactone	
Aliskiren	Aliskiren			
Antidyslipidemic agents				
Ezetimibe	Ezetimibe			
Fibrate	Bezafibrate	Gemfibrozil	Fenofibrate	
Statin	Simvastatin	Pravastatin	Atorvastatin	Pitavastatin
	Lovastatin	Fluvastatin	Rosuvastatin	
Antidiabetic agents				
Sulfonylurea	Glibenclamide (glyburide)	Gliquidone	Glimepiride	
	Glipizide	Gliclazide		
Meglitinide	Repaglinide	Nateglinide		
α-Glucosidase inhibitor	Acarbose			
Biguanide	Metformin			
TZD	Rosiglitazone	Pioglitazone		
DPP-4 inhibitor	Sitagliptin	Vildagliptin	Saxagliptin	Linagliptin
Insulin	Insulin lispro	Regular insulin	Ultralente insulin	Insulin detemir
	Insulin aspart	NPH	Insulin glargine	regular
	Insulin glulisine	Lente insulin		30% + NPH 70%
Medications associated with increased bleeding tendency				
Anticancer agents with bleeding risk	Azathioprine	Pemetrexed	Vinblastine	Nilotinib
	Cyclophosphamide	5-FU (5-fluorouracil)	MTX	Sorafenib
	Carboplatin	Hydroxyurea	(methotrexate)	Sunitinib
	Cytarabine	6-MP (mercaptopurine)	Imatinib	Bevacizumab
			Dasatinib	
Anticoagulants (except for warfarin, dabigatran, rivaroxaban)	Dalteparin	Enoxaparin	Heparin	
Antiplatelets (except for aspirin)	Clopidogrel	Dipyridamole	Cilostazol	Iloprost
	Ticlopidine	Eptifibatide	Anagrelide	Sulfinpyrazone
	Ticagrelor	Tirofiban		
NSAID	Diclofenac	Meloxicam	Tiaprofenic acid	Rofecoxib
	Etodolac	Nabumetone	Ketorolac	Etoricoxib
	Ibuprofen	Naproxen	Acemetacin	Sulindac
	Indomethacin	Piroxicam	Celecoxib	Tenoxicam
	Meclofenamate	Sulindac		Tiaprofenic acid
Fibrinolytic agents	Streptokinase	Urokinase		
Steroids	Betamethasone	Dexamethasone	Hydrocortisone	Prednisolone
	Cortisone	Fludrocortisone	Methylprednisolone	Triamcinolone
Ginkgo, Pentoxifylline, Piracetam	Ginkgo, pentoxifylline, piracetam			
Medications associated with decreased bleeding tendency				
Coagulation factor	Factor IX Complex, factors II, VII, IX, X, PCC	Anti-inhibitor—coagulant complex (factors II, VIIa, IX, X)	Plasma protein fraction	Coagulation factor VIIa

Please cite this article in press as: Hu M-M, et al., Factors driving the use of warfarin and non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation, Journal of the Formosan Medical Association (2016), http://dx.doi.org/10.1016/j.jfma.2016.05.007

(*continued*)

Medication	Generic names			
Tranexamic acid	Tranexamic acid			
H_2 blocker	Cimetidine Ranitidine	Famotidine	Nizatidine	Roxatidine
PPI	Omeprazole Pantoprazole	Lansoprazole Rabeprazole	Esomeprazole	Dexlansoprazole
Vitamin K	Vitamin K			

ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blocker; DHP-CCB = dihydropyridine calcium channel blocker; DPP-4 inhibitor = dipeptidyl peptidase-4 inhibitor; H_2 blocker = histamine type 2 receptor blocker; non-DHP-CCB = nondihydropyridine calcium channel blocker; NSAID = nonsteroidal anti-inflammatory drug; PPI = proton pump inhibitor; TZD = thiazolidinedione.

References

1. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: full text: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 guidelines for the management of patients with atrial fibrillation) developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Europace* 2006;**8**:651—745.
2. Zimetbaum PJ, Thosani A, Yu HT, Xiong Y, Lin J, Kothawala P, et al. Are atrial fibrillation patients receiving warfarin in accordance with stroke risk? *Am J Med* 2010;**123**:446—53.
3. Palm F, Kleemann T, Dos Santos M, Urbanek C, Buggle F, Safer A, et al. Stroke due to atrial fibrillation in a population-based stroke registry (Ludwigshafen Stroke Study) CHADS(2), CHA(2) DS(2)-VASc score, underuse of oral anticoagulation, and implications for preventive measures. *Eur J Neurol* 2013;**20**:117—23.
4. Hsieh FI, Lien LM, Chen ST, Bai CH, Sun MC, Tseng HP, et al. Get With the Guidelines-Stroke performance indicators: surveillance of stroke care in the Taiwan Stroke Registry: Get With the Guidelines-Stroke in Taiwan. *Circulation* 2010;**122**:1116—23.
5. Lin LJ, Cheng MH, Lee CH, Wung DC, Cheng CL, Yang YHK. Compliance with antithrombotic prescribing guidelines for patients with atrial fibrillation — a nationwide descriptive study in Taiwan. *Clin Ther* 2008;**30**:1726—36.
6. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;**361**:1139—51.
7. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;**365**:883—91.
8. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;**365**:981—92.
9. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;**369**:2093—104.
10. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 2014;**383**:955—62.
11. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland Jr JC, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2014;**64**:e1—76.
12. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J* 2012;**33**:2719—47.
13. Olesen JB, Sorensen R, Hansen ML, Lamberts M, Weeke P, Mikkelsen AP, et al. Non-vitamin K antagonist oral anticoagulation agents in anticoagulant naive atrial fibrillation patients: Danish nationwide descriptive data 2011—2013. *Europace* 2015;**17**:187—93.
14. Larsen TB, Rasmussen LH, Skjoth F, Due KM, Callreus T, Rosenzweig M, et al. Efficacy and safety of dabigatran etexilate and warfarin in "real-world" patients with atrial fibrillation: a prospective nationwide cohort study. *J Am Coll Cardiol* 2013;**61**:2264—73.
15. Bjerring Olesen J, Gislason GH, Torp-Pedersen C, Lip GY. Atrial fibrillation and vascular disease—a bad combination. *Clin Cardiol* 2012;**35**:S15—20.
16. Chao TF, Liu CJ, Wang KL, Lin YJ, Chang SL, Lo LW, et al. Using the CHA2DS2-VASc score for refining stroke risk stratification in 'low-risk' Asian patients with atrial fibrillation. *J Am Coll Cardiol* 2014;**64**:1658—65.
17. Chen PC, Lip GY, Yeh G, Lin HJ, Chien KL. Risk of bleeding and stroke with oral anticoagulation and antiplatelet therapy in patients with atrial fibrillation in Taiwan: a nationwide cohort study. *PLoS One* 2015;**10**:e0125257.

Please cite this article in press as: Hu M-M, et al., Factors driving the use of warfarin and non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation, Journal of the Formosan Medical Association (2016), http://dx.doi.org/10.1016/j.jfma.2016.05.007