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ORIGINAL RESEARCH ARTICLE

Novel oral anticoagulant vs. warfarin in elderly atrial fibrillation patients with normal, mid-range, and reduced left ventricular ejection fraction

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Abstract

Aims Patients with concomitant atrial fibrillation (AF) and reduced left ventricular ejection fraction (LVEF) have poor prognosis. Outcomes of novel oral anticoagulant (NOAC) in elderly AF patients with normal, mid-range, and reduced LVEF were investigated.

Methods and results Data were retrieved from Chang Gung Research Database during 2010–2017 for patients with AF. We excluded patients with venous thromboembolism within 6 months, total knee/hip replacement and heart valve replacement within 6 months, end-stage renal disease, stroke/systemic embolism (SE)/death within 7 days, age <65 years old, or no records of LVEF. Primary outcomes were ischaemic stroke (IS)/SE, major bleeding, and death from any cause. There was a total of 50 035 elderly AF patients retrieved. After exclusion criteria, 9615 patients with normal LVEF $\geq$ 50%, 737 with mid-range LVEF 41–49%, and 908 with reduced LVEF $\leq$ 40% were studied. At end of follow-up, patients on NOAC had significantly reduced IS/SE compared with warfarin in LVEF $\geq$ 50% [adjusted hazard ration (aHR) 0.80, 95% confidence interval (CI) 0.71–0.89] and LVEF 41–49% (aHR 0.57, 95% CI 0.36–0.88) after adjusting for covariates, while there was no difference in LVEF $\leq$ 40%. Patients on NOAC had significantly reduced major bleeding in all LVEF groups. In addition, patients on NOAC had significantly reduced death compared with warfarin in LVEF $\geq$ 50% (aHR 0.81, 95% CI 0.67–0.98).

Conclusions In elderly AF patients $\geq$65 years, using NOAC was associated with lower IS/SE compared with warfarin in normal and mid-range LVEF but not in reduced LVEF. Using NOACs was associated with lower death compared with warfarin in normal LVEF.

Keywords Atrial fibrillation; Left ventricular ejection fraction; Anticoagulation

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Introduction

In the recent decades, atrial fibrillation (AF) has emerged as a global epidemic, affecting 1% of general population and impacting tens of millions of patients worldwide.[1] In patients $\geq$65 years, AF is the most important arrhythmia, and left ventricular systolic dysfunction is an important cause of heart failure (HF) leading to hospitalization.[2,3] Because both AF and reduced left ventricular ejection function (LVEF) have common risk factors such as diabetes mellitus, hypertension, and coronary artery disease, it is no surprise that these two disease entities frequently coexist, and the interplay of which significantly worsen long-term prognosis.[4,5]

Oral anticoagulation is recommended for stroke prevention in female AF patients with a CHA_2DS_2-VASc score of $\geq$3 and in male AF patients with a CHA_2DS_2-VASc score of $\geq$2

unless contraindicated.[6] In addition, oral anticoagulation should be considered for stroke prevention in female AF patients with a CHA_2DS_2-VASc score of 2 and in male AF patients with a CHA_2DS_2-VASc score of 1 considering individual characteristics and patient preferences.[6] Recent landmark trials of novel oral anticoagulant (NOAC) have shown benefits of lower ischaemic stroke (IS), systemic embolism (SE), and major bleeding comparing with warfarin[7–10]; therefore, patients have been shifted to NOAC based on guideline recommendations.[11]

According to the 2016 European Society of Cardiology HF guidelines, patients with HF and LVEF $<$ 40% are categorized as HF with reduced ejection fraction (HFrEF), with a new distinct category of HF with LVEF 40–49% designated as HF with mid-range ejection fraction.[12] The impact of AF in HFrEF was not demonstrated to be influential for outcomes as in patients with LVEF $>$ 40%.[13] Therefore, to test the effectiveness and safety of NOAC vs. warfarin for stroke prevention in AF, we separated patients into normal LVEF $\geq$ 50%, mid-range LVEF 41–49%, and reduced LVEF $\leq$ 40%.[14]

Methods

Data source

In this retrospective cohort study, patient data were obtained from the largest healthcare provider in Taiwan, Chang Gung Memorial Hospital System, comprising three tertiary-care medical centres and four major teaching hospitals.[15–18] The healthcare provider has more than 10 000 beds and admits more than 280 000 patients servicing approximately one-tenth of the Taiwanese population each year. The hospital identification number of each patient was encrypted and de-identified to protect their privacy. Therefore, informed consent was waived for this study. The diagnosis and laboratory data could be linked and continuously monitored using consistent data encryption. The institutional review board of Chang Gung Memorial Hospital approved the study protocol (Institutional Review Board No. 201801428B0).

Study patients

By searching electronic medical records from the Chang Gung Research Database (CGRD) between 1 January 2010 and 31 December 2017, we retrieved patients with diagnosis of AF, using at least one inpatient or two outpatient claims for non-valvular AF. We excluded patients with deep vein thrombosis or pulmonary embolism within 6 months, total knee replacement or total hip replacement within 6 months, heart valve replacement within 6 months, and end-stage renal disease. In addition, we excluded patients with stroke, or SE, death within 7 days, or age $<$65 years old because our national health insurance system only reimburses the use of NOACs in patients with age $\geq$65. In addition, we excluded patients with no records of LVEF.

Study outcomes and follow-up

Primary outcomes were defined as IS/SE, major bleeding, and death from any cause.[19] The major bleeding was defined according to principle or secondary diagnosis of hospitalization and emergency visit and any blood transfusion order, which included admission for any bleeding, required blood transfusion $>$2 U, and life-threatening bleeding or vital organ haemorrhage, which included intracerebral haemorrhage. The follow-up period was defined as the period from the index date until the occurrence of study outcome, date of up to 5 years of follow-up, or the end date of the study period (31 December 2018), whichever came first. We censored patients if medications are switched or death before end date of follow-up. For patients with medication switched, we initiated second observation episode after medication switch as another group. Therefore, there were two records in the medication switched patients as two groups. While NOACs have shorter terminal elimination half-life ($t_{1/2}$), warfarin has $t_{1/2}$ of 1 week[20]; we therefore determined that an outcome event occurred within 7 days be attributed to the anticoagulation switch. Death was defined as in-hospital death or discharge against medical advice by terminal status from discharge report and/or emergence department records.

Disease was detected using International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) and ICD-10 codes. Covariates included age, sex, haemoglobin level, platelet count, estimated glomerular filtration rate, cholesterol, low-density lipoprotein cholesterol, aspartate transaminase (AST), alanine aminotransferase (ALT), and total bilirubin. In addition, co-morbidity of CHA_2DS_2-VASC score, HAS-BLED score, chronic liver disease, congestive HF, diabetes mellitus, hypertension, prior stroke, prior transient ischaemic attack, prior myocardial infarction, peripheral artery occlusive disease, history of percutaneous intervention, history of coronary artery bypass graft, history of bleeding, cancer, and peptic ulcer disease, medications at index date, and the use of NOAC and warfarin were retrieved.

Statistical analysis

We compared the baseline characteristics, co-morbidities, and medication, CHA_2DS_2-VASc score, and HAS-BLED score between the study groups using *t*-test for continuous variable or χ^2 test for categorical variable. We compared the risk of study outcomes between groups using Kaplan–Meier method with log-rank test and Cox proportional hazard model. We generated the plot of cumulative probability using Kaplan–

Meier method for time-to-event outcomes. Because there are three outcomes in this study, if a person died during study before an event of IS/SE or major bleeding, he or she will be censored. A multiple testing adjustment *P* value <0.027 was considered to be statistically significant. No adjustment of multiple testing (multiplicity) was made in this study. All statistical analyses were performed using commercial software (SAS 9.4, SAS Institute, Cary, NC). In multivariate Cox proportional hazard model, adjusted hazard ratio (aHR) was calculated after adjustment of age, sex, hypertension, diabetes mellitus, chronic liver disease, history of peptic ulcer disease, history of myocardial infarction, history of peripheral artery occlusive disease, history of transient ischaemic attack, history of IS/SE, history of bleeding, statins, amiodarone, non-steroidal anti-inflammatory drug, proton pump inhibitor, beta-blockers, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, digoxin, calcium channel blockers, aspirin, clopidogrel, ticagrelor, HF, and estimated glomerular filtration rate <60 mL/min/1.73 m^2.

Sensitivity analysis

In order to validate our study findings and check for robustness the study, we performed the sensitivity analysis. First, a sensitivity analysis is performed with events occurred within 14 days after a medication switch. Second, additional sensitivity analysis is performed with only events occurred within 7 days after the first anticoagulation switch, completed with competing risk. This second sensitivity analysis only analyse the first medication switch, which means events occurred were only attributed to the initial anticoagulation drug but not the second anticoagulation or third anticoagulation drug and so on if the patients had multiple medication switches.

Results

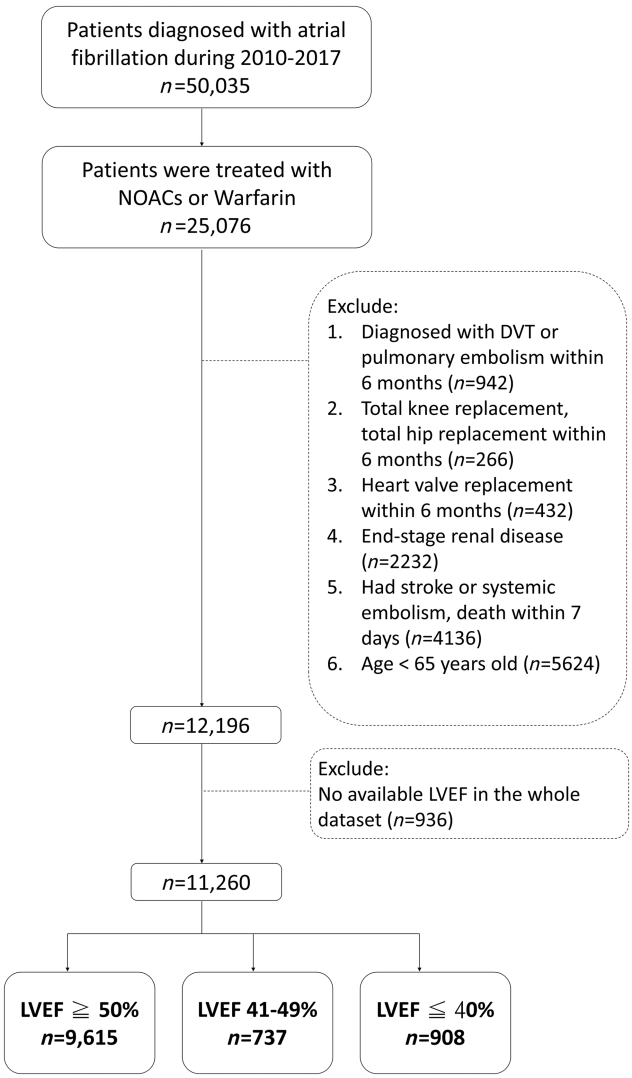
Study population

There were 50 035 patients with a principal diagnosis of AF between 2010 and 2017 identified in the CGRD. After exclusion criteria, the remaining patients totalled 11 260. There were 9615 patients with normal LVEF $\geq$ 50%, 737 patients with mid-range LVEF 41–49%, and 908 patients with reduced LVEF $\leq$ 40% (*Figure 1*). There was a total of 7815 patients using NOAC, with 27.49% (2148/7815) dabigatran, 44.64% (3489/7815) rivaroxaban, 18.99% (1484/7815) apixaban, and 8.88% (694/7815) edoxaban, and there was a total of 4878 patients using warfarin. The baseline characteristics of the study patients are shown in *Table 1*. Certain number of patients may have medication switch; therefore, prescription overlaps. However, there were a total of 6158 (no switch of medication) + 261 (switch of medication) = 6419 patients using NOAC, and there were a total of 3081 (no switch of medication) + 1760 (switch of medication) = 4841 patients using warfarin that were finally analysed. Patients were followed up at mean duration of 23 months (and maximal up to 60 months). Baseline characteristics of patients on NOAC or warfarin therapy are given in Supporting Information, *Table S1*.

Primary outcomes

In terms of IS/SE at end of follow-up, patients on NOAC had significantly lower events compared with patients on warfarin

Figure 1 Study design and screening criteria flow chart for the inclusion of elderly patients ≥65 years with atrial fibrillation and left ventricular ejection fraction (LVEF) groups. DVT, deep vein thrombosis; NOACs, novel oral anticoagulants.



in LVEF ≥ 50% [aHR 0.80, 95% confidence interval (CI) 0.71–0.89, $P < 0.001$] and LVEF 41–49% (aHR 0.57, 95% CI 0.36–0.88, $P = 0.019$) after adjusting for covariates. Patients on NOAC however had no significant difference compared with patients on warfarin in the group of LVEF ≤ 40% (aHR 0.91, 95% CI 0.61–1.35, $P = 0.637$) (*Table 2*). Cumulative incidence analysis also showed that there was significantly lower IS/SE in patients with LVEF ≥ 50% and LVEF 41–49% but not LVEF ≤ 40% (*Figure 2A*).

In terms of major bleeding at end of follow-up, patients on NOAC had significantly lower events compared with patients on warfarin in all LVEF groups (LVEF ≥ 50%, 41–49%, and ≤40% with $P < 0.001$, $P = 0.015$, and $P < 0.001$, respectively) (*Table 2*). Cumulative incidence analysis also showed that there was significantly lower major bleeding in patients in all LVEF groups (*Figure 2B*).

In addition, in terms of death from any cause at end of follow-up, patients on NOAC had significantly reduced death compared with warfarin in LVEF ≥ 50% (aHR 0.81, 95% CI 0.67–0.98, $P = 0.0358$). Patients on NOAC was not significantly different compared with patients on warfarin in LVEF 41–49% and LVEF ≤ 40% groups ($P = 0.353$ and $P = 0.563$, respectively) (*Table 2*). Kaplan–Meier also showed that there was significantly lower death from any cause in patients in LVEF ≥ 50% but not in LVEF 41–49% and LVEF ≤ 40% (*Figure 2C*).

Sensitivity analysis

Our first sensitivity analysis, which was performed with events occurred within 14 days after a medication switch, showed similar finding to the main analysis. At end of follow-up, patients on NOAC had significantly reduced IS/SE compared with warfarin in LVEF ≥ 50% (aHR 0.81, 95% CI 0.72–0.91, $P = 0.0003$) and LVEF 41–49% (aHR 0.59, 95% CI 0.37–0.90, $P = 0.0189$), while there was no difference in LVEF ≤ 40%. Patients on NOAC had significantly reduced major bleeding in all LVEF groups. In addition, patients on NOAC had no difference of death compared with warfarin in all LVEF (Supporting Information, *Table S2*).

Second sensitivity analysis is performed with only events occurred within 7 days after the first anticoagulation switch, completed with competing risk. At end of follow-up, patients on NOAC had significantly reduced IS/SE compared with warfarin in LVEF ≥ 50% (aHR 0.85, 95% CI 0.75–0.96, $P = 0.0102$), while there was no difference in LVEF 41–49% and LVEF ≤ 40%. Patients on NOAC had significantly reduced major bleeding in LVEF ≥ 50% (aHR 0.59, 95% CI 0.53–0.65, $P < 0.0001$) and LVEF ≤ 40% (aHR 0.40, 95% CI 0.28–0.58, $P < 0.0001$) but not LVEF 41–49%. In addition, patients on NOAC significantly reduced death compared with warfarin in LVEF ≥ 50% (aHR 0.76, 95% CI 0.61–0.94, $P = 0.0103$) but not in LVEF 41–49% and LVEF ≤ 40% (Supporting Information, *Table S3*).

Discussion

To our knowledge, this is the first study to investigate the efficacy and safety of NOAC vs. warfarin at mean follow-up of 24 months (up to maximal follow-up of 60 months) in ≥65-year-old patients with normal, mid-range, and reduced LVEF. Our study had the following findings: (i) for IS/SE prevention in AF, patients on NOAC only had benefit in LVEF groups of ≥50% and 41–49%. However, there was no significant difference in IS/SE prevention in AF in patients with reduced LVEF ≤ 40%. (ii) The benefit of major bleeding was observed consistently in AF patients in all LVEF groups. (iii) There was no difference of death from all cause in AF patients in all LVEF groups.

The interests in using NOAC instead of warfarin in stroke prevention have grown over recent decade with the publications of four landmark trials. Because left ventricular systolic dysfunction with reduced LVEF is a frequently encountered co-morbidity of AF, its influence on patients with AF and subsequent outcome has been a subject of investigation. In the four major trials of NOAC, only two performed subgroup analysis regarding to HF. In the trial of dabigatran vs. warfarin in patients with AF, the authors reported that there was benefit efficacy with significantly lower IS/SE in dabigatran 150 mg vs. warfarin but not in dabigatran 110 mg in patients with HF, defined as LVEF < 40% or New York Heart Association Class II or higher, HF symptoms within 6 months before screening.[7] In the trial of apixaban vs. warfarin in patients with AF, the authors showed that there was efficacy of significantly lower IS/SE in patients with HF, defined as symptomatic HF or LVEF < 40%.[9] In addition, there was no safety difference on major bleeding between patients with or without HF.[9] In this current study, we have included patients using all four of NOACs.

A new distinct HF category of HF with mid-range ejection fraction was designated to stimulate research into the underlying characteristics, pathophysiology, and potential for treatment of this segment of population.[12] Although the optimal treatment for mid-range LVEF remains uncertain, it is presumably similar to patients with preserved LVEF.[12] On the other hand, patients with reduced LVEF had historically been conducted with ample of clinical trials where evidence-based therapies are more established.[12] In the recently published paper by Heart Failure Association of European Society of Cardiology, the influence of AF or sinus rhythm (SR) on patients with reduced LVEF < 40% did not lead to difference on the adverse events, whether or not it was acute or chronic HF,[13] suggesting the reduced LVEF itself was more important than the impact of AF. And in patients with mid-range LVEF, those with AF had significantly more adverse events than those with SR in acute HF, while there was no difference between AF or SR in chronic HF. The authors postulated plausible explanation for the differential association of AF with adverse cardiovascular outcome between the LVEF groups

Table 1 Baseline characteristics of anticoagulated atrial fibrillation patients

	All	LVEF			*P* value
		≥50%	41–49%	≤40%	
No. of patients	11 260	9615	737	908	
Age at index date, mean (SD)	76.36 (7.25)	76.32 (7.23)	76.66 (7.43)	77 (7.29)	0.2844
65–74, *n* (%)	4846 (43.04)	4164 (43.31)	306 (41.52)	376 (41.41)	0.3844
75–84, *n* (%)	4719 (41.91)	4029 (41.9)	309 (41.93)	381 (41.96)	
≥85, *n* (%)	1695 (15.05)	1422 (14.79)	122 (16.55)	151 (16.63)	
Female, *n* (%)	5358 (47.58)	4694 (48.82)	309 (41.93)	355 (39.10)	<0.0001
Haemoglobin, g/L	12.12 (1.96)	12.15 (1.96)	11.87 (1.87)	12.02 (2.00)	0.0007
Platelet, $\times 10^3/\mu L$	195.3 (66.78)	195.5 (65.25)	200.50 (85.28)	188.60 (64.40)	0.0034
eGFR, mL/min/1.73 m^2	69.08 (25.72)	69.75 (25.46)	63.65 (25.50)	65.75 (28.09)	<0.0001
eGFR < 60 mL/min/1.73 m^2; *n* (%)	5900 (52.4)	4879 (50.74)	463 (62.82)	558 (61.45)	<0.0001
Total cholesterol, mg/dL	163.7 (31.85)	164.5 (31.62)	158.30 (32.35)	158.50 (33.19)	<0.0001
LDL cholesterol, mg/dL	91.94 (26.85)	91.72 (26.54)	91.46 (28.67)	94.77 (28.57)	0.2210
AST	44.44 (218.7)	40.12 (141.5)	63.33 (364.30)	74.18 (518.70)	<0.0001
ALT	30.78 (94.41)	28.65 (75.07)	35.54 (88.28)	49.16 (209.00)	<0.0001
Total bilirubin	0.9 (0.77)	0.89 (0.66)	0.86 (0.62)	1.03 (1.49)	0.0005
Co-morbidity at index date					
CHA_2DS_2-VASc score, mean (SD)	3.71 (1.67)	3.67 (1.66)	3.90 (1.69)	3.94 (1.70)	<0.0001
HAS-BLED score, mean (SD)	3.18 (1.11)	3.19 (1.10)	3.15 (1.12)	3.08 (1.10)	0.0083
Chronic liver disease, *n* (%)	1728 (15.35)	1527 (15.88)	94 (12.75)	107 (11.78)	0.0006
Congestive heart failure, *n* (%)	4396 (39.04)	3190 (33.18)	481 (65.26)	725 (79.85)	<0.0001
Diabetes mellitus, *n* (%)	2696 (23.94)	2309 (24.01)	180 (24.42)	207 (22.80)	0.6788
Hypertension, *n* (%)	6218 (55.22)	5424 (56.41)	372 (50.47)	422 (46.48)	<0.0001
Prior stroke, *n* (%)	2194 (19.48)	1878 (19.53)	150 (20.35)	166 (18.28)	0.5474
Prior TIA, *n* (%)	381 (3.38)	326 (3.39)	23 (3.12)	32 (3.52)	0.8994
Prior myocardial infarction, *n* (%)	2236 (19.86)	1696 (17.64)	222 (30.12)	318 (35.02)	<0.0001
PAOD, *n* (%)	255 (2.26)	201 (2.09)	20 (2.71)	34 (3.74)	0.0041
History of PCI, *n* (%)	450 (4)	326 (3.39)	63 (8.55)	61 (6.72)	<0.0001
History of CABG, *n* (%)	114 (1.01)	68 (0.71)	17 (2.31)	29 (3.19)	<0.0001
History of bleeding, *n* (%)	4608 (40.92)	4005 (41.65)	280 (37.99)	323 (35.57)	0.0004
Cancer	1471 (13.06)	1267 (13.18)	87 (11.80)	117 (12.89)	0.5589
Digoxin	2272 (20.18)	1685 (17.52)	218 (29.58)	369 (40.64)	<0.0001
Peptic ulcer	3435 (30.51)	2994 (31.14)	211 (28.63)	230 (25.33)	0.0007
Medications at index date					
NSAIDs, *n* (%)	6107 (54.24)	5303 (55.15)	361 (48.98)	443 (48.79)	<0.0001
Beta-blockers, *n* (%)	6444 (57.23)	5348 (55.62)	481 (65.26)	615 (67.73)	<0.0001
Calcium channel blockers, *n* (%)	3634 (32.27)	3134 (32.59)	237 (32.16)	263 (28.96)	0.0818
ACEi or ARB, *n* (%)	6610 (58.7)	5449 (56.67)	498 (67.57)	663 (73.02)	<0.0001
Loop diuretics, *n* (%)	4148 (36.84)	3185 (33.13)	374 (50.75)	589 (64.87)	<0.0001
PPIs, *n* (%)	2513 (22.32)	2113 (21.98)	188 (25.51)	212 (23.35)	0.0629
Statins, *n* (%)	3211 (28.52)	2687 (27.95)	229 (31.07)	295 (32.49)	0.0042
Amiodarone, *n* (%)	3159 (28.06)	2581 (26.84)	245 (33.24)	333 (36.67)	<0.0001
Medications after index date					
NOAC, *n* (%)	7815 (69.41)	6736 (70.06)	476 (64.59)	603 (66.41)	0.0010
Apixaban 5 mg, *n* (%)	1484 (13.18)	1255 (13.05)	101 (21.22)	128 (21.23)	0.6124
Dabigatran 110 mg, *n* (%)	1946 (17.28)	1688 (17.56)	123 (25.84)	135 (22.39)	0.1115
Dabigatran 150 mg, *n* (%)	202 (1.79)	177 (1.84)	10 (2.10)	15 (2.49)	0.5995
Edoxaban 30 mg, *n* (%)	459 (4.08)	390 (4.06)	25 (5.25)	44 (7.30)	0.3219
Edoxaban 60 mg, *n* (%)	235 (2.09)	198 (2.06)	14 (2.94)	23 (3.81)	0.5925
Rivaroxaban 10 mg, *n* (%)	786 (6.98)	669 (6.96)	49 (10.29)	68 (11.28)	0.7811
Rivaroxaban 15 mg, *n* (%)	1920 (17.05)	1674 (17.41)	110 (23.11)	136 (22.55)	0.0500
Rivaroxaban 20 mg, *n* (%)	783 (6.95)	685 (7.12)	44 (9.24)	54 (8.96)	0.2281
Warfarin, *n* (%)	4878 (43.32)	4096 (42.6)	357 (48.44)	425 (46.81)	0.0007
TTR, mean (SD)	28.73 (22.13)	28.88 (21.70)	26.24 (22.13)	29.27 (27.01)	0.5665
Aspirin, *n* (%)	4783 (42.48)	3968 (41.27)	388 (52.65)	427 (47.03)	<0.0001
Clopidogrel, *n* (%)	2325 (20.65)	1817 (18.9)	241 (32.70)	267 (29.41)	<0.0001
Ticagrelor, *n* (%)	207 (1.84)	158 (1.64)	26 (3.53)	23 (2.53)	0.0003
NSAIDs, *n* (%)	4042 (35.9)	3587 (37.31)	225 (30.53)	230 (25.33)	<0.0001
Beta-blockers, *n* (%)	7835 (69.58)	6455 (67.13)	614 (83.31)	766 (84.36)	<0.0001
Calcium channel blockers, *n* (%)	3940 (34.99)	3471 (36.1)	250 (33.92)	219 (24.12)	<0.0001
ACEi or ARB, *n* (%)	7838 (69.61)	6454 (67.12)	609 (82.63)	775 (85.35)	<0.0001
Loop diuretics, *n* (%)	5901 (52.41)	4624 (48.09)	525 (71.23)	752 (82.82)	<0.0001
PPIs, *n* (%)	3368 (29.91)	2840 (29.54)	252 (34.19)	276 (30.40)	0.0275
Statins, *n* (%)	4063 (36.08)	3418 (35.55)	301 (40.84)	344 (37.89)	0.0078
Amiodarone, *n* (%)	4358 (38.7)	3575 (37.18)	342 (46.40)	441 (48.57)	<0.0001
Follow-up time (months)					

(*Continues*)

Table 1 (continued)

	All	LVEF ≥50%	LVEF 41–49%	LVEF ≤40%	*P* value
Ischaemic stroke/systemic embolism	31.69 (25.00)	31.88 (25.13)	31.72 (24.60)	29.60 (23.78)	0.0314
Major bleeding	26.92 (23.42)	26.99 (23.54)	27.29 (23.18)	25.83 (22.36)	0.3282
Death from any cause	38.48 (25.01)	38.81 (25.19)	38.23 (23.99)	35.23 (23.71)	0.0002
Overall	23.11 (22.67)	23.14 (22.76)	23.56 (22.74)	22.43 (21.63)	0.5677

ACEi, angiotensin-converting enzyme inhibitor; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; AST, aspartate transaminase; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; NOAC, novel oral anticoagulant; NSAID, non-steroidal anti-inflammatory drug; PAOD, peripheral artery occlusive disease; PCI, percutaneous coronary intervention; PPIs, proton pump inhibitors; SD, standard deviation; TIA, transient ischaemic attack; TTR, time in therapeutic range.

and suggested that with higher LVEF, AF may contribute to progression of HF and worsen outcomes, whereas with lower LVEF, the HF disease itself and its severity determine the outcomes.[13]

Atrial fibrillation with reduced LVEF frequently coexist, and each likely to complicate the course of the other with no clear consensus on how to best treat these patients.[21] In this scenario, our study also showed a pattern of treatment efficacy by NOAC vs. warfarin in both LVEF ≥ 50% and LVEF 41–49% patient groups. Our study also showed that in LVEF ≤ 40%, the treatment efficacy of NOAC vs. warfarin worn off because the HF severity itself determines the outcome but not AF and is consistent with the previous study. On the other hand, our study further showed that treatment safety by events major bleeding was significantly lower in all LVEF groups, suggesting that NOAC should be prioritized for lower bleeding events regardless of LVEF.

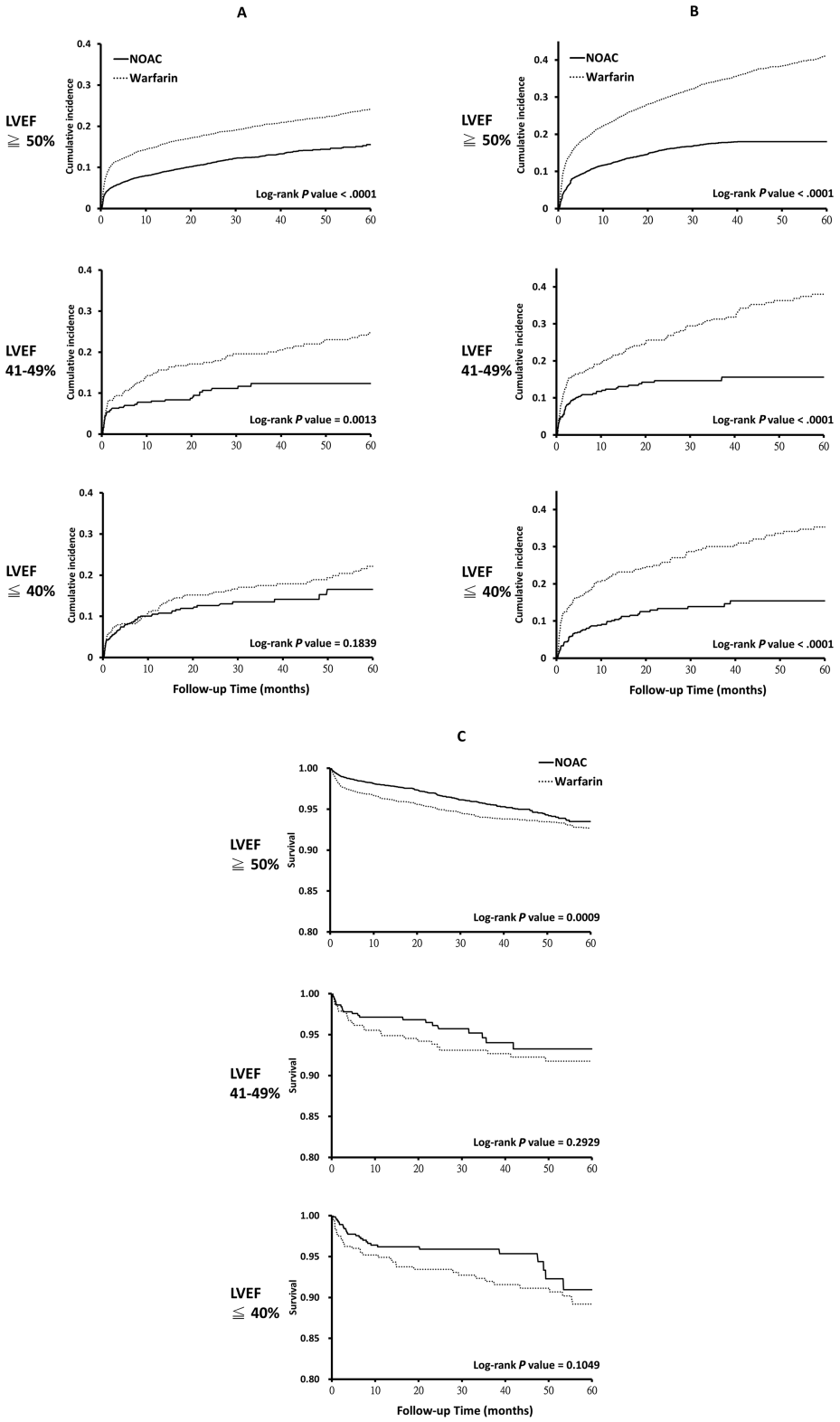
Our sensitivity analyses have similar finding. The first sensitivity analysis, which was performed with events occurred within 14 days after a medication switch, showed similar finding to the main analysis. At end of follow-up, patients on NOAC had significantly reduced IS/SE compared with warfarin in LVEF ≥ 50% and LVEF 41–49%, while there was no difference in LVEF ≤ 40%. Patients on NOAC had significantly reduced major bleeding in all LVEF groups. However, patients on NOAC had no difference of death compared with warfarin in all LVEF. Second sensitivity analysis is performed with only events occurred within 7 days after the first anticoagulation switch, completed with competing risk. At end of follow-up, patients on NOAC had significantly reduced IS/SE compared with warfarin in LVEF ≥ 50%, while there was no difference in LVEF 41–49% and LVEF ≤ 40%. Patients on NOAC had significantly reduced major bleeding in LVEF ≥ 50% and LVEF ≤ 40% but not LVEF 41–49%. In addition, patients on

Table 2 Events that occurred within 7 days of medication switch are counted towards the adverse event relating to the first medication used

Event type	Group	Drug	No. of events	Total year	Incidence rate (per 100 person-years)	Crude hazard ratio; *P* value	Adjusted hazard ratio; *P* value
Ischaemic stroke/systemic embolism	≥50%	NOAC	725	13 535	5.36	0.58 (0.53–0.64); <0.0001	0.75 (0.68–0.84); <0.0001
		Warfarin	863	11 942	7.23	1	1
	41–49%	NOAC	47	943	4.99	0.55 (0.38–0.79); 0.0014	0.65 (0.43–0.97); 0.0483
		Warfarin	73	1005	7.26	1	1
	≤40%	NOAC	71	1099	6.46	0.80 (0.58–1.12); 0.1808	0.88 (0.62–1.26); 0.4840
		Warfarin	72	1134	6.35	1	1
Major bleeding	≥50%	NOAC	920	11 496	8.00	0.45 (0.41–0.49); <0.0001	0.54 (0.50–0.60); <0.0001
		Warfarin	1412	10 060	14.04	1	1
	41–49%	NOAC	59	805	7.33	0.47 (0.34–0.64); <0.0001	0.65 (0.45–0.92); 0.0156
		Warfarin	108	871	12.39	1	1
	≤40%	NOAC	67	1018	6.58	0.42 (0.31–0.57); <0.0001	0.47 (0.34–0.64); <0.0001
		Warfarin	113	931	12.14	1	1
Death from any cause	≥50%	NOAC	252	16 098	1.57	0.74 (0.62–0.89); 0.0014	0.81 (0.67–0.98); 0.0385
		Warfarin	266	14 999	1.77	1	1
	41–49%	NOAC	22	1110	1.98	0.74 (0.41–1.31); 0.3026	0.76 (0.38–1.47); 0.4091
		Warfarin	26	1237	2.10	1	1
	≤40%	NOAC	28	1329	2.11	0.66 (0.40–1.09); 0.1150	0.83 (0.48–1.42); 0.5117
		Warfarin	36	1336	2.69	1	1

NOAC, novel oral anticoagulant.

Figure 2 Cumulative incidence of (A) ischaemic stroke/systemic embolism, (B) major bleeding, and (C) death from any cause, in elderly atrial fibrillation patients on novel oral anticoagulant (NOAC) compared with warfarin with normal left ventricular ejection fraction (LVEF) ≥50%, mid-range LVEF 41–49%, and reduced LVEF ≤ 40%.



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NOAC significantly reduced death compared with warfarin in LVEF $\geq$ 50% but not in LVEF 41–49% and LVEF $\leq$ 40%.

In patients with reduced LVEF $<$ 40%, the left ventricular systolic dysfunction itself is already an important prognosticator for poor outcome of mortality or HF hospitalization irrespective of AF or SR.[12] However, in our study, the results showed that a novel and improved anticoagulation drug, NOAC, did not improve its efficacy outcome of IS/SE comparing with warfarin in patients with LVEF $\leq$ 40%. In addition, NOAC did not improve death from any cause compared with warfarin in LVEF $<$ 50%. A theoretically improved anticoagulated state did not lead to corresponding improved prevention of IS/SE in these groups of patients with mid-range and normal LVEF and prevention of death in normal 50%. This is to caution us that in patients with HFrEF, HF *per se* may be the most important prognostic predictor instead of rhythm disturbance as AF. Our finding is compatible with the results from European Society of Cardiology Heart Failure Long-Term Registry.[13] In summary, this is the first study to investigate the efficacy and safety of NOAC vs. warfarin in patients with AF and normal, mid-range, and reduced LVEF, and further studies are required to understand the effect of NOAC in patients with reduced LVEF.

Limitations

There are several limitations in epidemiologic data from NHIRD. First, using ICD-9-CM and ICD-10 codes for patient screening may result in sources of bias for conditions not coded correctly. Second, because of the limitation of CGRD medical records, clinical symptoms may not be a reliable source of factors to evaluate these patients; therefore, claim-based diagnosis, examinations, medications, procedures, clinical visits, and hospital admissions and discharges were used in preference to symptoms. Third, it is a retrospective, non-randomized cohort study with all its inherent limitations (e.g. selection bias and reporting bias). Fourth, we did not analyse individual NOACs to delineate the efficacy and safety of each drug compared with warfarin because the number of more recently introduced edoxaban users was relatively small. Last, our study was conducted in patients with nearly homogenous ethnic background, and application of our results to other populations warrants further studies.

Conclusions

In elderly AF patients ≥65 years, using NOAC was associated with lower IS/SE compared with warfarin in normal and mid-range LVEF but not in reduced LVEF. Using NOACs was associated with lower death from any cause compared with warfarin in these patients with normal LVEF.

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Conflict of interest

None declared.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Baseline characteristics of anticoagulated atrial fibrillation patients.

Table S2. *Events that occurred within 14 days of medication switch are counted toward the adverse event relating to the first medication used.*

Table S3. *Events that occurred within 7 days of medication switch are counted toward the adverse event relating to only the first medication (not 2nd or 3rd medications if there were.*

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