


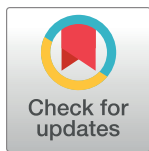
RESEARCH ARTICLE

Efficacy and safety of NOAC versus warfarin in AF patients with left atrial enlargement

Victor Chien-Chia Wu ^{1,2}, Chun-Li Wang^{1,2}, Shu-Ting Gan³, Michael Wu⁴, Shao-Wei Chen⁵, Chang-Fu Kuo^{2,6,7}, Yu-Tung Huang ³, Ming-Shien Wen^{1,2}, Shang-Hung Chang^{1,2,3,8*}

1 Division of Cardiology, Chang Gung Memorial Hospital, Linkou Medical Center, Taoyuan City, Taiwan, **2** College of Medicine, Chang Gung University, Taoyuan City, Taiwan, **3** Center for Big Data Analytics and Statistics, Chang Gung Memorial Hospital, Linkou Medical Center, Taoyuan City, Taiwan, **4** Division of Cardiovascular Medicine, Arrhythmia Services Section, Rhode Island Hospital, Warren Alpert School of Medicine, Brown University, Providence, Rhode Island, United States of America, **5** Department of Cardiothoracic and Vascular Surgery, Chang Gung Memorial Hospital, Linkou Medical Center, Taoyuan City, Taiwan, **6** Division of Rheumatology, Allergy and Immunology, Department of Internal Medicine, Chang Gung Memorial Hospital, Linkou Medical Center, Taoyuan City, Taiwan, **7** Division of Rheumatology, Orthopaedics and Dermatology, School of Medicine, University of Nottingham, Nottingham, United Kingdom, **8** Graduate Institute of Nursing, Chang Gung University of Science and Technology, Taoyuan City, Taiwan

* afen.chang@gmail.com


 OPEN ACCESS

Citation: Wu VC-C, Wang C-L, Gan S-T, Wu M, Chen S-W, Kuo C-F, et al. (2020) Efficacy and safety of NOAC versus warfarin in AF patients with left atrial enlargement. PLoS ONE 15(12): e0243866. <https://doi.org/10.1371/journal.pone.0243866>

Editor: Hans-Peter Brunner-La Rocca, Maastricht University Medical Center, NETHERLANDS

Received: March 30, 2020

Accepted: November 29, 2020

Published: December 14, 2020

Copyright: © 2020 Wu et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: The data is owned by the third party, Chang Gung Memorial Hospital, by analyzing data from Chang Gung Research Database (CGRD). Gaining access to data in CGRD can be achieved by contacting Chang Gung Memorial Hospital Center for Big Data Analytics and Statistics (<https://www1.cgmh.org.tw/rccr/>). Interested researchers can replicate our study findings in their entirety by directly obtaining the data from CGRD and following the protocol in your Methods section. Authors in this study do not have

Abstract

Background

Little is known about the effects of anticoagulation in patients with atrial fibrillation (AF) and left atrial enlargement (LAE).

Methods

Data of patients with AF were retrieved from Chang Gung Research Database during 2007–2016. We excluded patients who were not using oral anticoagulants, used anticoagulants for <30 days, used ≥ 2 agents concomitantly or switched anticoagulants, had left atrial diameter missing from their data, were aged <65, had received valve surgeries, had mitral stenosis, or had a history of cancer. The primary outcomes were ischemic stroke (IS)/systemic embolism (SE), major bleeding, and death from any cause.

Results

We identified 40,777 patients who received a diagnosis of AF. After the exclusion criteria were applied, 6,445 patients remained, 4,922 with LAE, and they were followed up for 2.4 ± 1.9 years. The mean age of the patients was 77.32 ± 0.18 in the NOAC group and 76.58 ± 6.91 in the warfarin group ($p < 0.0001$); 48.24% of patients in the NOAC group and 46.98% of patients in the warfarin group were men ($p > 0.05$). The mean CHA₂DS₂-VASc score was 3.26 ± 1.05 in the NOAC group and 3.07 ± 1.12 in the warfarin group ($p < 0.0001$). The mean HAS-BLED score was 3.87 ± 3.81 in the NOAC group and 3.86 ± 3.80 in the warfarin group ($p > 0.05$). Furthermore, the mean LA diameter was 4.75 ± 0.63 cm in the warfarin group and 4.79 ± 0.69 cm in the warfarin group ($p > 0.05$). Among patients with LAE, NOAC was associated with significantly reduced IS/SE events (CRR = 0.63, 95% CI = 0.52–0.77),

any special access privileges that others would not have.

Funding: Funded by Center for Big Data Analytics and Statistics Grants, CORPG3G0271 and CLRPG3D0045, at Chang Gung Memorial Hospital, for Dr. Shang-Hung Chang. The funder plays role in the study design and monitor, data analysis and interpretation.

Competing interests: The authors have declared that no competing interests exist.

no difference in major bleeding (CRR = 0.91, 95% CI = 0.78–1.05), and significantly reduced death from any cause (aHR = 0.65, 95% CI = 0.52–0.80) compared with warfarin.

Conclusions

In elderly patients with AF and LAE, NOAC was associated with reduced IS/SE and death from any cause compared with warfarin, whereas no difference in major bleeding was observed between these treatments.

Introduction

Patients with atrial fibrillation (AF) are treated with anticoagulation for stroke prevention based on their CHA₂DS₂-VASc risk score [1,2]. However, the risk of ischemic stroke (IS) in these patients remains substantial even with the appropriate use of anticoagulation following the guideline recommendations, suggesting that other factors are at play. One critical contributor is left atrium size, which has been described as a risk factor for nonvalvular AF [3,4]. Increased left atrial size has been demonstrated to reflect the AF disease duration and burden [5,6]. Notably, studies have demonstrated that left atrial enlargement (LAE), independent of CHA₂DS₂-VASc score, is also a risk predictor for IS [7–10].

Despite the remarkable benefits of warfarin and novel vitamin K-antagonist oral anticoagulants (NOAC) in reducing stroke risk and mortality in patients with AF, the residual stroke risk was 1.7% and 1.4% per year among patients receiving warfarin and NOACs, respectively, at the end of a 2.2-year follow-up [11]. A study on therapeutic anticoagulation treatment for IS among patients with AF reported that moderate to severe LAE was associated with treatment failure [12]. Landmark trials on NOACs versus warfarin were conducted in patients with AF with high stroke risk based on CHAD₂ score [13–16]. These studies did not conclude whether NOACs are associated with more favorable outcomes compared with warfarin in patients with AF marked by normal or enlarged left atrial (LA) size. Therefore, we investigated the efficacy and safety profiles of NOAC and warfarin in patients with AF with LAE.

Methods

Data source

In this retrospective cohort study, patient data were obtained from the Chang Gung Memorial Hospital System, which is the largest health care provider in Taiwan, comprising three major teaching hospitals and four tertiary-care medical centers [13–16]. This health care provider has over 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 deidentified to protect their privacy. Informed consent was thus waived for this study. The diagnosis and laboratory data were linked and continuously monitored using consistent data encryption. The Institutional Review Board of Chang Gung Memorial Hospital approved the study protocol (IRB No. 201802093B0).

Data availability statement

The data are owned by Chang Gung Memorial Hospital and were obtained for analysis from the Chang Gung Research Database (CGRD). Data in the CGRD can be accessed by contacting the Chang Gung Memorial Hospital Center for Big Data Analytics and Statistics (<https://>

www1.cgmh.org.tw/rcctr/). Therefore, researchers can replicate the study findings in their entirety by directly obtaining the data from CGRD and following the protocol presented in the Methods section. The authors of this study do not have any special access privileges.

Study patients

A search of the electronic medical records of the CGRD between January 1, 2007, and December 31, 2016, yielded data from patients with a diagnosis of AF based on at least one inpatient or two outpatient claims for nonvalvular AF. Patients who were not receiving oral anticoagulants (e.g., warfarin, dabigatran, rivaroxaban, apixaban, or edoxaban) or had an anticoagulation use <30 days, had concomitant use of ≥ 2 agents, switched the oral anticoagulant used, had missing LA diameter data, had a history of valve surgery, had mitral stenosis, or had a history of cancer were excluded. Furthermore, patients aged <65 years were excluded because Taiwan's National Health Insurance only reimburses NOAC prescriptions for patients aged ≥ 65 years. The included patients, diagnosed as having AF and using oral anticoagulants, were separated into patients with normal LA size and patients with LAE.

Definition of LAE

Based on the 2015 American Society of Echocardiography guidelines on Recommendations for Cardiac Chamber Quantification in Adults, normal anteroposterior LA diameters are 2.7–3.8 cm in women and 3.0–4.0 cm in men [17]. Therefore, LAE was defined as anteroposterior diameters of >3.8 cm in women and >4.0 cm in men in this study.

Study outcomes and follow-up

Primary outcomes were defined as IS/systemic embolism (SE), major bleeding, and death from any cause at the end of follow-up [18]. Major bleeding was defined based on principal or secondary diagnosis at hospitalizations and emergency visits and any blood transfusion order, including admission for any bleeding, a need for a blood transfusion of >2 U, and life-threatening bleeding or vital organ hemorrhage (e.g., intracerebral hemorrhage). The follow-up period was defined as the period from the index date until the first occurrence of any study outcome or the end date of the study period (December 31, 2016), whichever came first.

We applied the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) and ICD-10 codes to categorize diseases. Covariates included age, sex, CHA₂DS₂-VAsC score, HAS-BLED score, LA size, comorbidities, and medications. The comorbidities included were diabetes mellitus, hypertension, heart failure, renal insufficiency, peptic ulcer disease, abnormal liver function, peripheral artery disease, and old myocardial infarction. The medications included were antiplatelets, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, amiodarone/dronedarone, beta blockers, calcium channel blockers, diuretics, NSAIDs, and antidiabetic drugs.

Statistical analysis

The *t* test was used to assess continuous variables, and the χ^2 test was used to assess categorical variables. The propensity score was included as a covariate based on the CHA₂DS₂-VAsC and HAS-BLED scores. The risk of death from any cause was compared between groups using a Cox proportional hazards model. Competing risk regression (CRR) was performed with IS/SE and major bleeding. A *p* value <0.05 was considered statistically significant. No adjustments for multiple testing (multiplicity) were used in this study. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

Sensitivity analysis

Two sensitivity analyses were performed to validate our study findings and assess selection biases. In the first analysis, patients who were not using oral anticoagulants, such as warfarin, dabigatran, rivaroxaban, apixaban, or edoxaban, or had not used anticoagulants for <90 days were excluded; the other exclusion criteria remained the same. In the second analysis, outcome analyses were performed based on left atrial diameter (LAD) indexed to body surface area (BSA). A study reported that the LAD index value of normal control was $20 \pm 3 \text{ mm/m}^2$ (mean \pm SD) [19]. The LAD index $> 26 \text{ mm/m}^2$ indicated dilated when 26 mm/m^2 (mean $+ 2\text{SD}$) was used as the cutoff value.

Results

Study population

We identified 40,777 patients with a principal diagnosis of AF during 2007–2016 in the CGRD. After exclusion criteria, a group of 6,445 patients remained. LAE was present in a total of 4,922 patients that comprise the study population (Fig 1 and Table 1). The mean follow-up time was 2.4 ± 1.9 years. The time in therapeutic range was assessed based on an international normalized ratio between 2.0 and 3.0, which revealed that the warfarin therapy quality was 44.81% in the study patients. The mean age of the patients was 77.32 ± 0.18 in the NOAC group and 76.58 ± 6.91 in the warfarin group ($p < 0.0001$), with 48.24% men in the NOAC group and 46.98% men in the warfarin group ($p = \text{ns}$). The mean CHA₂DS₂-VASc score was 3.26 ± 1.05 in the NOAC group and 3.07 ± 1.12 in the warfarin group ($p < 0.0001$). The mean HAS-BLED score was 3.87 ± 3.81 in the NOAC group and 3.86 ± 3.80 in the warfarin group ($p = \text{ns}$). Furthermore, LA diameter was 4.76 ± 0.63 cm in the NOAC group and 4.79 ± 0.69 cm in the warfarin group ($p = \text{ns}$). Overall, patients in the NOAC group were significantly older and had significantly higher CHA₂DS₂-VASc scores, reflecting a high risk of stroke.

Primary outcomes

In patients with LAE, patients receiving NOAC had a significantly lower number of IS/SE events (CRR: 0.63, 95% CI: 0.52–0.77, $p < 0.001$) (Table 2 and Fig 2) at the end of follow-up compared with patients receiving warfarin. Cumulative incidence analysis revealed a significantly lower number of IS/SE events in the NOAC group ($p = 0.0005$) (Fig 3A). Patients receiving NOAC displayed no difference in major bleeding compared with patients receiving warfarin (CRR: 0.91, 95% CI: 0.78–1.05, $p = 0.190$). Cumulative incidence analysis revealed no difference in major bleeding between the groups ($p = 0.5613$) (Fig 3B). Furthermore, compared with patients receiving warfarin, patients receiving NOAC had significantly reduced death from any cause (adjusted hazard ratio [aHR]: 0.65, 95% CI: 0.52–0.80, $p < 0.001$). Kaplan–Meier survival analysis revealed significantly reduced death from any cause in the NOAC group ($p = 0.0003$) (Fig 3C). Based on our major findings, we calculated the observed (post hoc) power to be as follows: IS/SE, 0.82; major bleeding, 0.08; and death from any cause, 0.84.

Sensitivity analysis

The first sensitivity analysis indicated that patients receiving NOAC had significantly reduced IS/SE at the end of follow-up compared with patients receiving warfarin (CRR: 0.60, 95% CI: 0.48–0.76) (S1 Table). Patients receiving NOAC displayed no difference in major bleeding compared with patients receiving warfarin (CRR: 0.86, 95% CI: 0.73–1.02), but they displayed significantly reduced death from any cause (aHR: 0.68, 95% CI: 0.54–0.85).

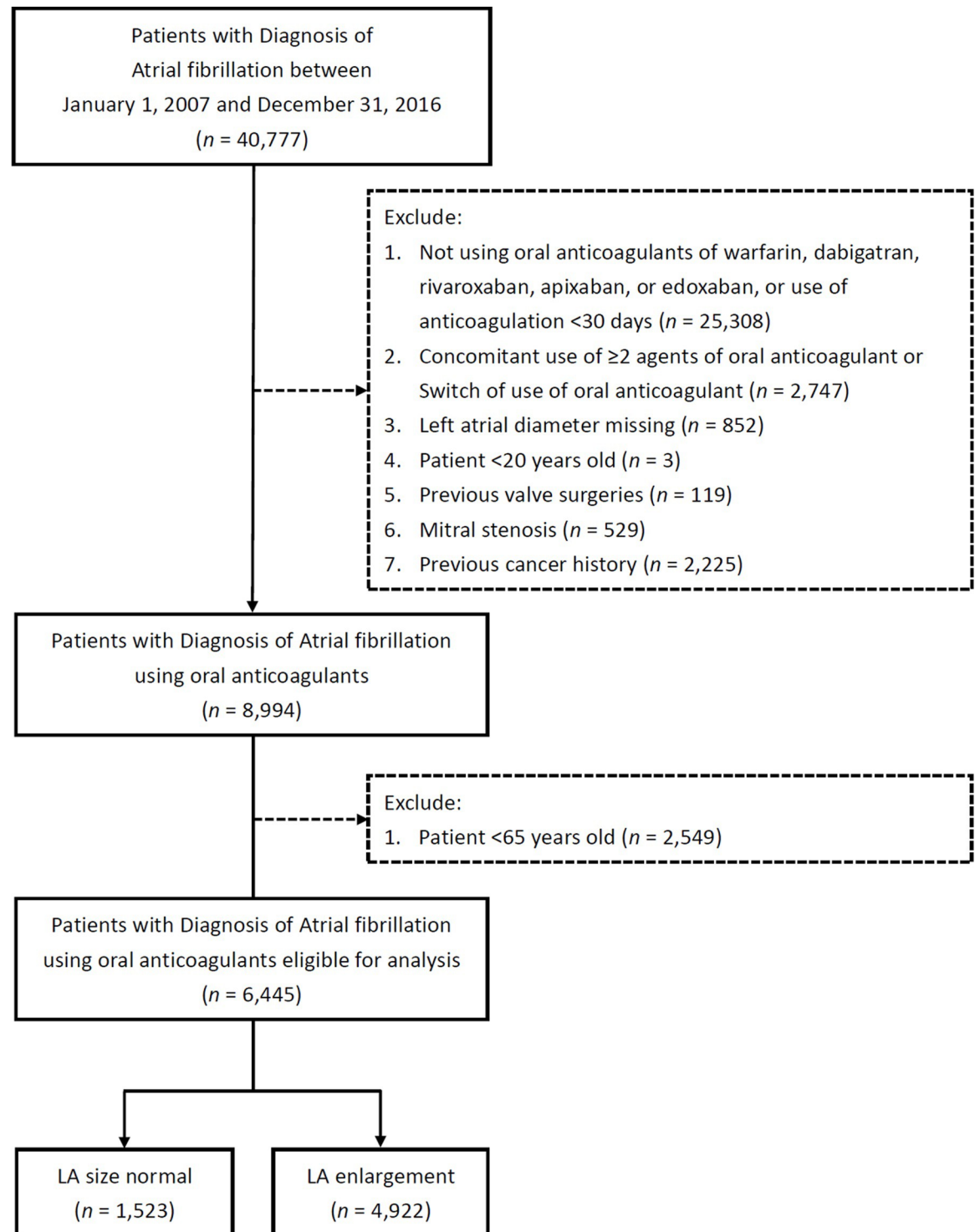


Fig 1. Study design and screening criteria flowchart for the inclusion of elderly AF patients with LAE. AF, atrial fibrillation; LA, left atrial enlargement.

<https://doi.org/10.1371/journal.pone.0243866.g001>

In the second sensitivity analysis, a LAD index $> 26 \text{ mm/m}^2$ was considered dilated. After excluding patients with missing BSA data, data from 1,430 patients were analyzed (NOAC

Table 1. Baseline characteristics of study patients.

	LAE				Test
	NOAC (n = 1,592)		Warfarin (n = 1,592)		
	Median	IQR	Median	IQR	
Age	77	72–83	76	71–81	<i>p</i> -value*
CHA ₂ DS ₂ -VASc score	3	3–4	3	2–4	<0.001
	Mean	SD	Mean	SD	<i>p</i> -value†
HAS-BLED score	3.87	1.21	3.86	1.19	0.859
LA size	4.76	0.63	4.79	0.69	0.185
	N	%	N	%	<i>p</i> -value‡
Male	768	48.24	748	46.98	0.478
Comorbidities					
Diabetes mellitus	555	34.86	524	32.91	0.246
Hypertension	1302	81.78	1101	69.16	< .0001
Heart failure	729	45.79	750	47.11	0.456
Renal insufficiency	496	31.16	506	31.78	0.703
Peptic ulcer disease	283	17.78	286	17.96	0.890
Abnormal liver function	164	10.30	173	10.87	0.604
Peripheral artery disease	23	1.44	45	2.83	0.007
Old myocardial infarction	103	6.47	122	7.66	0.189
Medications					
Antiplatelets	458	28.77	452	28.39	0.814
ACEi/ARB	486	30.53	492	30.90	0.818
Amiodarone/dronedarone	513	32.22	498	31.28	0.568
Beta blockers	454	28.52	477	29.96	0.370
Calcium channel blockers	308	19.35	296	18.59	0.588
Diuretics	399	25.06	415	26.07	0.516
NSAIDs	169	10.62	175	10.99	0.732
Antidiabetic drug	217	13.63	231	14.51	0.476

IQR, interquartile range; SD, standard deviation.

* Wilcoxon rank-sum test.

† independent t test.

‡ χ^2 test.

<https://doi.org/10.1371/journal.pone.0243866.t001>

group: 749 patients, warfarin group: 681 patients). Patients with a dilated LAD index receiving NOAC displayed significantly reduced IS/SE at the end of follow-up compared with those receiving warfarin (CRR: 0.61, 95% CI: 0.41–0.90) (**S1 Table**). Patients receiving NOAC had no difference in major bleeding compared with patients receiving warfarin (CRR: 0.90, 95% CI: 0.69–1.18). Furthermore, death from any cause was significantly reduced among patients receiving NOAC compared with patients receiving warfarin (aHR: 0.69, 95% CI: 0.51–0.95).

Discussion

To our knowledge, this is the first study to investigate and compare the outcomes of NOAC compared with warfarin in elderly patients with AF aged ≥ 65 years with normal and enlarged LA sizes; key findings are as follows: Patients with LAE receiving NOAC were associated with significantly reduced IS/SE events and deaths from any cause, without differences in major bleeding compared with patients with LAE receiving warfarin.

Table 2. Hazard ratios for outcomes in patients with LAE.

Ischemic stroke/Systemic embolism						
Drug	Patients	Events	Incidence	Crude HR	Adjusted HR	Competing Risk HR
NOAC	1,253	130	10.38	0.67 (0.54–0.84)*	0.66 (0.53–0.83)*	0.63 (0.52–.77)*
Warfarin	1,161	209	18.00	1	1	1
Major bleeding						
Drug	Patients	Events	Incidence	Crude HR	Adjusted HR	Competing Risk HR
NOAC	1,378	255	18.51	0.95 (0.80–1.13)	0.95 (0.80–1.12)	0.91 (0.78–1.05)
Warfarin	1,348	325	24.11	1	1	
Death from any cause						
Drug	Patients	Events	Incidence	Crude HR	Adjusted HR	Competing Risk HR
NOAC	1,466	134	9.14	0.67 (0.54–0.83)*	0.65 (0.52–0.80)*	
Warfarin	1,425	278	19.51	1	1	

Model adjusted for CHA₂DS₂-VASc and HAS-BLED scores; $p < 0.05$.

HR, hazard ratio; LA, left atrial; NOAC, novel vitamin K-antagonist oral anticoagulant.

<https://doi.org/10.1371/journal.pone.0243866.t002>

The risk of thromboembolism, resulting in stroke and systemic arterial occlusion, in patients with AF is a major concern, and treatment guidelines are continually updated to offer more precise approaches to predicting and preventing these events [20–22]. The CHA₂DS₂-VASc score was developed as an improvement on the CHAD₂ score for more accurate risk prediction and anticoagulation guidance [23]. Landmark trials of NOACs versus warfarin were based on risk assessment by using CHAD₂ score [24–27]. However, few AF guidelines have addressed the effect of LAE on stroke risk or accounted for AF in stroke risk score calculation. Furthermore, LA size was not mentioned in the landmark trials, even though LAE was a clear marker of AF disease status and a predictor of stroke risk [3–10].

The mechanisms of the increased risk of stroke in patients with LAE remains poorly understood. However, left atrium dilation is associated with the loss of atrial pump function and an increase in blood stasis, which in turn predispose the patient to LA thrombus formation and embolization [28]. The thrombogenicity of LA dilation was also confirmed in transesophageal echocardiography studies that reported that LAE was associated with increased spontaneous echo contrast, LA thrombus formation, and embolic events [29]. Thus, these results suggest a potential causal relationship between LAE and subsequent thromboembolism and stroke.

A study to determine the residual stroke rate, which is often regarded as treatment failure, compared patients with AF receiving anticoagulation treatment with a matched control population with comparable baseline risks and without AF [30]. The cumulative mortality at 1.5 years was 4.2% in patients with AF receiving warfarin and 2.5% in the matched controls, even after adjustment for baseline differences ($p = 0.005$) [30]. This residual mortality risk may be attributed to additional AF stroke risk factors that were not accounted for in the traditional CHA₂DS₂-VASc scores, such as LA size [7–10]. Furthermore, reduced LA size was demonstrated to have protective effects against AF and AF-associated complications by reducing the inducibility and duration of AF [31].

In this study, we investigated whether the residual stroke risk associated with LAE was more improved by taking NOAC rather than warfarin in terms of efficacy, safety, and mortality profiles. Elderly patients with AF (≥ 65 years old) with LAE were studied. Our results revealed that NOAC had consistent benefits over warfarin, with significantly reduced IS/SE and death from any cause in patients with LAE or LAD index dilatation. Furthermore, no difference in major bleeding was observed between patients with LAE or LAD index

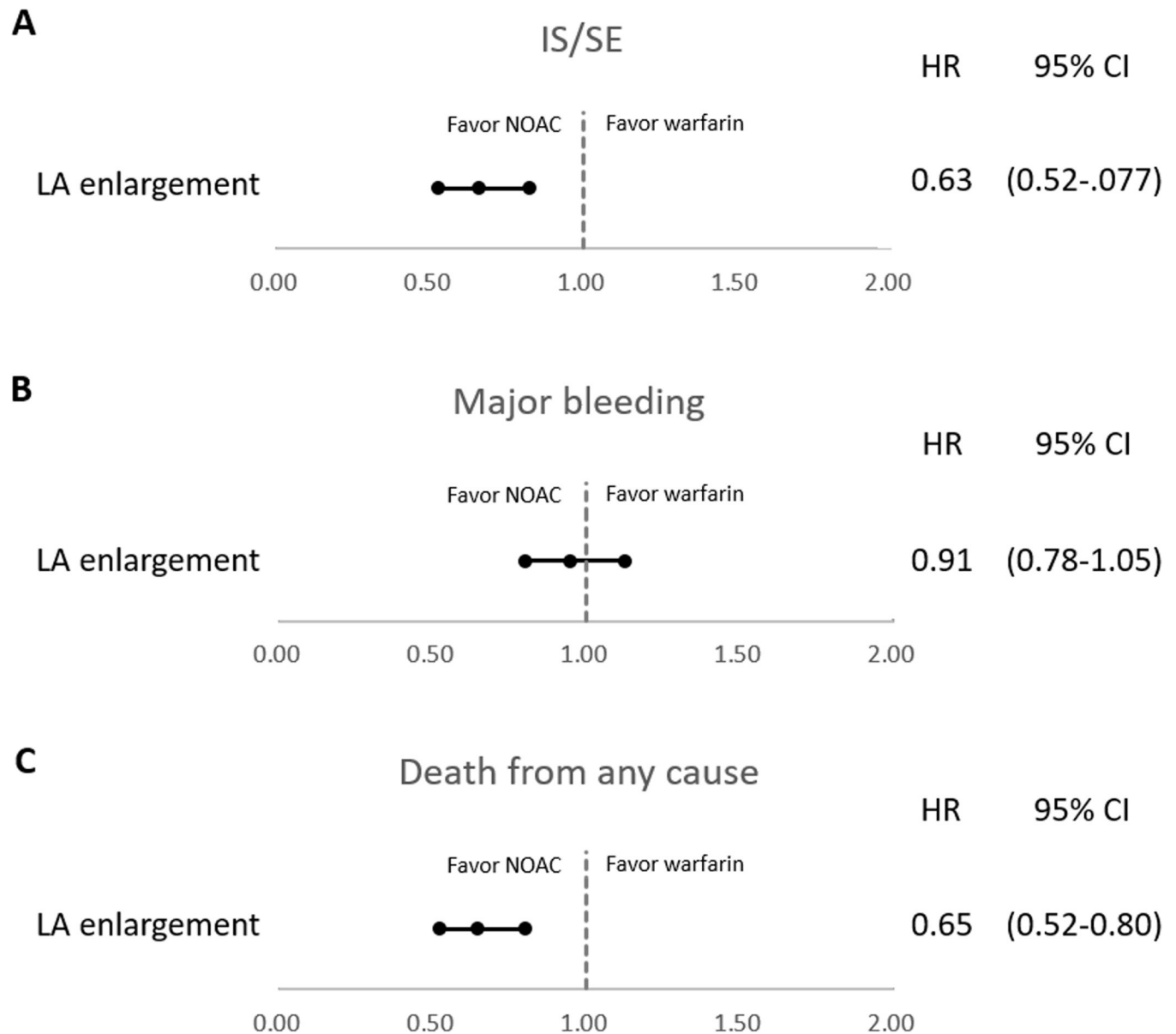


Fig 2. Primary outcomes that occurred during follow-up. (A) IS/SE, (B) major bleeding, (C) death from any cause. CI, confidence interval; HR, hazard ratio; IS/SE, ischemic stroke/systemic embolism.

<https://doi.org/10.1371/journal.pone.0243866.g002>

dilatation taking NOAC or warfarin. Anticoagulation treatment failure has been encountered in patients with AF with marked LAE [12], and our study revealed that NOAC may confer mortality benefits compared with warfarin in patients with LAE. In the first sensitivity analysis, we excluded patients who had treatment times with anticoagulants of <90 days, and the results were similar to the main study, which excluded patients with treatment times with anticoagulants of <30 days. In the second sensitivity analysis, in which we performed outcome analysis based on the LAD index, the results were also similar to the main study. The strength of the current study provides important real-world data that confirm the superiority of NOACs compared to warfarin to reduce the risk for stroke in patients with AF.

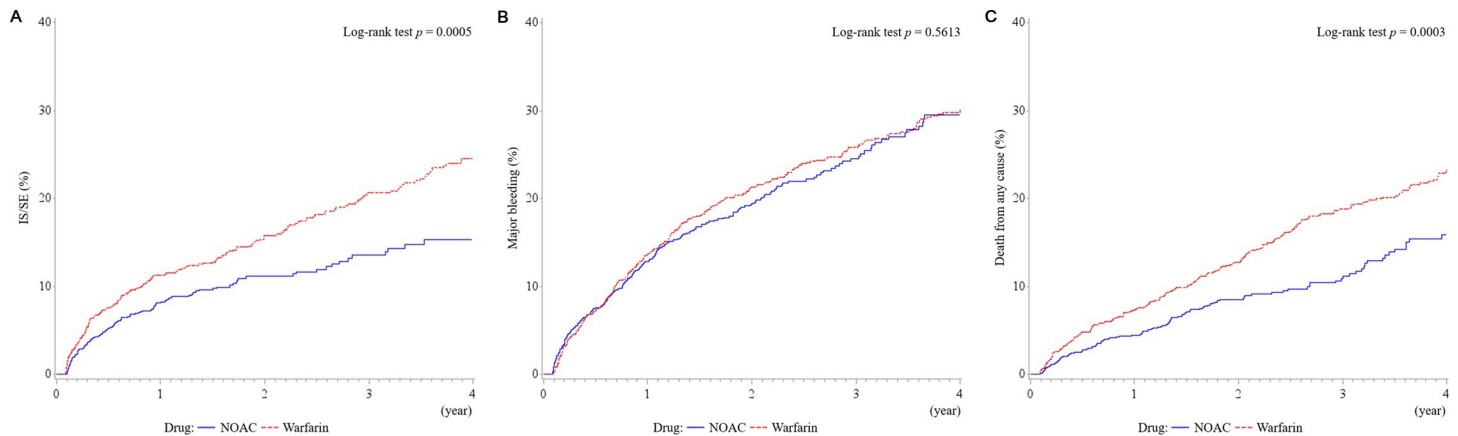


Fig 3. Cumulative incidence of IS/SE (A), major bleeding (B), and Kaplan–Meier survival analysis of death from any cause (C) in elderly patients with AF with LAE treated with NOAC and warfarin.

<https://doi.org/10.1371/journal.pone.0243866.g003>

In summary, compared with warfarin, the use of NOAC was associated with reduced IS/SE and mortality events in elderly patients with AF and LAE. Further studies are warranted to clarify the role of LAE among current AF stroke risk scores.

Limitations

Epidemiologic data from the CGRD have several limitations. First, the use of ICD-9-CM and ICD-10 codes may lead to missing cases of patient conditions that were incorrectly coded. Second, we did not analyze individual NOACs to delineate the efficacy and safety of each drug compared with warfarin because the number of recently introduced edoxaban users was relatively small. Third, we only included patients aged ≥ 65 years because Taiwan's National Health Insurance does not reimburse the NOAC prescriptions of patients aged < 65 years, which may have resulted in selection bias. However, most patients develop AF in older age. Therefore, our study likely still represents the majority of patients with AF in Taiwan. Fourth, the data retrieved from the CGRD represent patients with more severe disease status than patients from regional hospitals or local clinics because these data were obtained from teaching hospitals and tertiary medical centers within the Chang Gung Memorial Hospital System. Fifth, since the current study has a non-randomized retrospective design, the results should be treated with a certain caution and should be considered hypothesis generating. Last, this study was conducted in an ethnically homogenous population; therefore, the application of the results in other populations may require further studies.

Conclusions

In elderly AF patients ≥ 65 years old with LAE, using NOAC was associated with reduced ischemic stroke/systemic embolism events as well as deaths from any cause compared with using warfarin, with no differences of major bleeding events.

Supporting information

S1 Table. Hazard ratios for outcomes in patients with LAE (follow-up > 90 days). (DOCX)

S2 Table. Hazard ratios for outcomes in patients with dilated LAD indexed to BSA (>26 mm/m²).
(DOCX)

Acknowledgments

The authors appreciate the statistical assistance and wish to acknowledge the support of the Maintenance Project of the Center for Big Data Analytics and Statistics at Chang Gung Memorial Hospital in study design and monitoring, data analysis, and interpretation.

Author Contributions

Conceptualization: Victor Chien-Chia Wu, Shang-Hung Chang.

Data curation: Victor Chien-Chia Wu, Chun-Li Wang, Shu-Ting Gan, Shang-Hung Chang.

Formal analysis: Victor Chien-Chia Wu, Shu-Ting Gan, Yu-Tung Huang, Shang-Hung Chang.

Funding acquisition: Shang-Hung Chang.

Supervision: Shao-Wei Chen, Chang-Fu Kuo, Yu-Tung Huang, Ming-Shien Wen, Shang-Hung Chang.

Writing – original draft: Victor Chien-Chia Wu, Chun-Li Wang, Michael Wu.

References

1. Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Eur Heart J* 2018; 39:1330–93. <https://doi.org/10.1093/eurheartj/ehy136> PMID: 29562325
2. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr, et al. 2019 AHA/ACC/HRS Focused Update of the 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 Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2019:S0735–1097:30209–8. <https://doi.org/10.1016/j.jacc.2019.01.011> [Epub ahead of print]. PMID: 30703431
3. Psaty BM, Manolio TA, Kuller LH, et al. Incidence of and risk factors for atrial fibrillation in older adults. *Circulation*. 1997; 96:2455–61. <https://doi.org/10.1161/01.cir.96.7.2455> PMID: 9337224
4. Tsang TS, Gersh BJ, Appleton CP, et al. Left ventricular diastolic dysfunction as a predictor for the first diagnosed nonvalvular atrial fibrillation in 840 elderly men and women. *J Am Coll Cardiol*. 2002; 40:1636–44. [https://doi.org/10.1016/s0735-1097\(02\)02373-2](https://doi.org/10.1016/s0735-1097(02)02373-2) PMID: 12427417
5. Gupta DK, Shah AM, Giugliano RP, Ruff CT, Antman EM, Grip LT, et al. Left atrial structure and function in atrial fibrillation: ENGAGE AF-TIMI 48. *Eur Heart J* 2014; 35:1457–65. <https://doi.org/10.1093/eurheartj/ehy500> PMID: 24302269
6. Hamatani Y, Ogawa H, Takabayashi K, Yamashita Y, Takagi D, Esato M, et al. Left atrial enlargement is an independent predictor of stroke and systemic embolism in patients with non-valvular atrial fibrillation. *Sci Rep* 2016; 6:31042. <https://doi.org/10.1038/srep31042> PMID: 27485817
7. Tiwari S, Løchen ML, Jacobsen BK, Hopstock LA, Nyrnes A, Njølstad I, et al. CHA₂DS₂-VASc score, left atrial size and atrial fibrillation as stroke risk factors in the Tromsø Study. *OpenHeart* 2016; 3:e000439. <https://doi.org/10.1136/openhrt-2016-000439> PMID: 27621829
8. Ogata T, Matsuo R, Kiyuna F, Hata J, Ago T, Tsuboi Y, et al. Left atrial size and long-term risk of recurrent stroke after acute ischemic stroke in patients with nonvalvular atrial fibrillation. *J Am Heart Assoc* 2017; 6:e006402. <https://doi.org/10.1161/JAHA.117.006402> PMID: 28862939
9. Maheshwari A, Norby FL, Roetker NS, Soliman EZ, Koene RJ, Rooney MR, et al. Refining Prediction of Atrial Fibrillation–Related Stroke Using the P2-CHA₂DS₂-VASc Score. *Circulation* 2019; 139:180–91. <https://doi.org/10.1161/CIRCULATIONAHA.118.035411> PMID: 30586710
10. Rapacciuolo A, Mancusi C, Canciello G, Izzo R, Strisciuglio T, de Luca N, et al. CHA₂DS₂-VASc score and left atrial volume dilatation synergistically predict incident atrial fibrillation in hypertension: an

- observational study from the Campania Salute Network registry. *Sci Rep* 2019; 9:7888. <https://doi.org/10.1038/s41598-019-44214-2> PMID: 31133712
11. Ruff CT, Giugliano RP, Braunwald E, 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. [https://doi.org/10.1016/S0140-6736\(13\)62343-0](https://doi.org/10.1016/S0140-6736(13)62343-0) PMID: 24315724
 12. Dakay K, Chang AD, Hemendinger M, Cutting S, McTaggart RA, Jayaraman MV, et al. Left Atrial Enlargement and Anticoagulation Status in Patients with Acute Ischemic Stroke and Atrial Fibrillation. *J Stroke Cerebrovasc Dis* 2018; 27:192–7. <https://doi.org/10.1016/j.jstrokecerebrovasdis.2017.08.025> PMID: 28918087
 13. Tsai MS, Lin MH, Lee CP, Yang YH, Chen WC, Chang GH, et al. Chang Gung Research Database: A multi-institutional database consisting of original medical records. *Biomd J* 2017; 40:263–9.
 14. Wang CL, Wu VC, Kuo CF, Chu PH, Tseng HJ, Wen MS, et al. Efficacy and Safety of Non-Vitamin K Antagonist Oral Anticoagulants in Atrial Fibrillation Patients With Impaired Liver Function: A Retrospective Cohort Study. *J Am Heart Assoc* 2018; 7:e0099263. <https://doi.org/10.1161/JAHA.118.009263> PMID: 30371232
 15. Wang CL, Wu VC, Lee CH, Kuo CF, Chen YL, Chu PH, et al. Effectiveness and safety of non-vitamin-K antagonist oral anticoagulants versus warfarin in atrial fibrillation patients with thrombocytopenia. *J Thromb Thrombolysis* 2019; 47:512–9. <https://doi.org/10.1007/s11239-018-1792-1> PMID: 30565148
 16. Wang CL, Wu VC, Huang YT, Kuo CF, Chu PH, Chen YL, et al. Safety and Effectiveness of Non-Vitamin K Antagonist Oral Anticoagulants for Stroke Prevention in Patients With Atrial Fibrillation and Anemia: A Retrospective Cohort Study. *J Am Heart Assoc*. 2019; 8:e012029. <https://doi.org/10.1161/JAHA.119.012029> PMID: 31020896
 17. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015; 28:1–39.e14.
 18. Koretsune Y, Etoh T, Katsuda Y, Suetsugu T, Kumeda K, Sakuma I, et al. Risk Profile and 1-Year Outcome of Newly Diagnosed Atrial Fibrillation in Japan—Insights From GARFIELD-AF. *Circ J* 2018; 83:67–74. <https://doi.org/10.1253/circj.CJ-18-0655> PMID: 30518731
 19. Yoshida C, Nakao S, Goda A, Naito Y, Matsumoto M, Otsuka M, et al. Value of assessment of left atrial volume and diameter in patients with heart failure but with normal left ventricular ejection fraction and mitral flow velocity pattern. *Eur J Echocardiogr* 2009; 10:278–81. <https://doi.org/10.1093/ejehocard/jen234> PMID: 18786948
 20. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016; 37:2893–962. <https://doi.org/10.1093/eurheartj/ehw210> PMID: 27567408
 21. Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation: executive summary. *Europace* 2018; 20:1231–42. <https://doi.org/10.1093/europace/euy054> PMID: 29562331
 22. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr, et al. 2019 AHA/ACC/HRS Focused Update of the 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 Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2019; 74:104–32. <https://doi.org/10.1016/j.jacc.2019.01.011> PMID: 30703431
 23. Lip GY, Nieuwlaar R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach. *Chest* 2010; 137:263–72. <https://doi.org/10.1378/chest.09-1584> PMID: 19762550
 24. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009; 361:1139–51. <https://doi.org/10.1056/NEJMoa0905561> PMID: 19717844
 25. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011; 365:883–91. <https://doi.org/10.1056/NEJMoa1009638> PMID: 21830957
 26. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011; 365:981–92. <https://doi.org/10.1056/NEJMoa1107039> PMID: 21870978
 27. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013; 369:2093–104. <https://doi.org/10.1056/NEJMoa1310907> PMID: 24251359
 28. Keren G., Etzion T., Sherez J., Zelcer A.A., Megidish R., Miller H.I., et al. Atrial fibrillation and atrial enlargement in patients with mitral stenosis. *Am. Heart J* 1987; 114:1146–55. [https://doi.org/10.1016/0002-8703\(87\)90190-6](https://doi.org/10.1016/0002-8703(87)90190-6) PMID: 2960225

29. Benjamin EJ, D'Agostino RB, Belanger AJ, Wolf PA, Levy D. Left atrial size and the risk of stroke and death. The Framingham Heart Study *Circulation*. 1995; 92:835–41. <https://doi.org/10.1161/01.cir.92.4.835> PMID: 7641364
30. Freedman B, Martinez C, Katholing A, Rietbrock S. Residual Risk of Stroke and Death in Anticoagulant-Treated Patients With Atrial Fibrillation. *JAMA Cardiol* 2016; 1:366–8. <https://doi.org/10.1001/jamacardio.2016.0393> PMID: 27438123
31. Li Y, Li WM, Gong YT, Li BX, Liu W, Han W, et al. The effects of cilazapril and valsartan on the mRNA and protein expressions of atrial calpains and atrial structural remodeling in atrial fibrillation dogs. *Basic Res Cardiol* 2007; 102:245–56. <https://doi.org/10.1007/s00395-007-0641-8> PMID: 17268887