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CLINICAL RESEARCH

Non-vitamin K antagonist oral anticoagulants in atrial fibrillation patients without previous oral anticoagulants or stable under warfarin: a nationwide cohort study

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Aims Investigations on non-VKA oral anticoagulants (NOACs) for atrial fibrillation (AF) patients without taking any oral anticoagulants (OACs) or staying well on warfarin were limited. We aimed to investigate the associations between stroke prevention strategies and clinical outcomes among AF patients who were previously well without taking any OACs or stayed well on warfarin for years.

Methods and results The retrospective analysis included a total of 54 803 AF patients who did not experience an ischaemic stroke or intra-cranial haemorrhage (ICH) for years after AF was diagnosed. Among these patients, 32 917 patients who did not receive OACs were defined as the 'original non-OAC cohort' (group 1), and 8007 patients who continuously received warfarin were defined as the 'original warfarin cohort' (group 2). In group 1, compared to non-OAC, warfarin showed no significant difference in ischaemic stroke (aHR 0.979, 95%CI 0.863–1.110, $P = 0.137$) while those initiated NOACs were associated with lower risk (aHR 0.867, 95%CI 0.786–0.956, $P = 0.043$). When compared to warfarin, the composite of 'ischaemic stroke or ICH' and 'ischaemic stroke or major bleeding' was significantly lower in the NOAC initiator with an aHR of 0.927 (95%CI 0.865–0.994; $P = 0.042$) and 0.912 (95%CI 0.837–0.994; $P < 0.001$), respectively. In group 2, when compared to warfarin, those shifted to NOACs were associated with a lower risk of ischaemic stroke (aHR 0.886, 95%CI 0.790–0.993, $P = 0.002$) and major bleeding (aHR 0.849, 95%CI 0.756–0.953, $P < 0.001$).

Conclusions The NOACs should be considered for AF patients who were previously well without taking OACs and those who were free of ischaemic stroke and ICH under warfarin for years.

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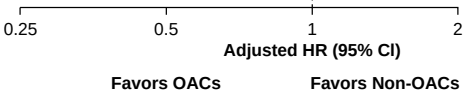
Graphical Abstract

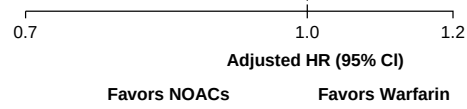
Group 1 : Non-OACs population from the diagnosis of AF to June 1st, 2015

OACs versus Non-OACs	Number of events (%/year)	Adjusted HR (95% CI)	*P* value
Ischemic stroke			
Non-OACs	1152 (1.158)	Ref	
Warfarin	8 (1.132)	0.979 (0.863–1.110)	0.137
NOACs	49 (1.032)	0.867 (0.786–0.956)	0.043
ICH			
Non-OACs	345 (0.345)	Ref	
Warfarin	1 (0.135)	0.569 (0.080–4.054)	0.573
NOACs	16 (0.331)	0.912 (0.565–1.471)	0.243
Major bleeding			
Non-OACs	2354 (2.394)	Ref	
Warfarin	14 (1.962)	0.578 (0.341–0.979)	< 0.001
NOACs	95 (2.023)	0.773 (0.627–0.952)	0.002
All-cause mortality			
Non-OACs	6598 (6.575)	Ref	
Warfarin	47 (6.368)	0.876 (0.773–0.992)	0.036
NOACs	305 (6.277)	0.798 (0.644–0.989)	0.047
Ischemic stroke or ICH			
Non-OACs	1248 (1.255)	Ref	
Warfarin	8 (1.132)	0.876 (0.757–1.013)	0.078
NOACs	53 (1.118)	0.844 (0.744–0.957)	< 0.001
Ischemic stroke or major bleeding			
Non-OACs	3012 (3.066)	Ref	
Warfarin	19 (2.675)	0.849 (0.729–0.989)	< 0.001
NOACs	110 (2.385)	0.789 (0.682–0.913)	< 0.001



Group 2: Warfarin population from the diagnosis of AF to June 1st, 2015

NOACs versus Warfarin	Number of events (%/year)	Adjusted HR (95% CI)	*P* value
Ischemic stroke			
Warfarin	108 (0.538)	Ref	
NOACs	20 (0.458)	0.886 (0.790–0.993)	0.002
ICH			
Warfarin	116 (0.539)	Ref	
NOACs	19 (0.432)	0.976 (0.841–1.132)	0.167
Major bleeding			
Warfarin	502 (2.407)	Ref	
NOACs	99 (2.347)	0.849 (0.756–0.953)	< 0.001
All-cause mortality			
Warfarin	1243 (5.736)	Ref	
NOACs	303 (6.853)	0.944 (0.832–1.07)	0.215
Ischemic stroke or ICH			
Warfarin	208 (0.968)	Ref	
NOACs	27 (0.619)	0.842 (0.763–0.929)	< 0.001
Ischemic stroke or major bleeding			
Warfarin	657 (3.157)	Ref	
NOACs	105 (2.501)	0.88 (0.784–0.986)	< 0.001



Keywords Atrial fibrillation • Warfarin • NOACs • Drug initiation • Drug shift

What's New?

- In AF patients without OACs, those initiated on NOACs were associated with a lower risk of ischaemic stroke and composite events.
- In AF patients who stayed well on warfarin for years, those who shifted to NOACs were still associated with better clinical outcomes.
- The NOACs should be considered for AF patients who were previously well without taking OACs and those who were free of ischaemic stroke and ICH under warfarin for years.

Introduction

One of the pillars of contemporary atrial fibrillation (AF) management is stroke prevention, where the default is to offer oral anticoagulation (OAC) unless the patient is 'truly low risk' of stroke.[1,2] The OAC is offered as a vitamin K antagonist (VKA, e.g. warfarin) or a non-VKA oral anticoagulant [NOAC, also referred to as a direct oral anticoagulant (DOAC)]. Indeed, stroke prevention is one aspect of holistic or integrated care management of AF, which is recommended in guidelines given the improved clinical outcomes with such an approach.[1–3]

Despite the increasing uptake of NOACs in everyday clinical practice, a common clinical practice dilemma was whether AF patients who have stayed well on warfarin for years should continue on their current regime or shift to NOACs. Another situation was the management of AF patients who were previously well without taking any OACs for years. These AF patients were 'survivors' free of serious adverse events causing hardship in persuading them to receive long-term OACs which were recommended in international guidelines. This study aimed to investigate how AF patients who were previously well without taking any OACs would fare if they continued untreated with no OACs or if they were started on warfarin or NOAC. Second, we investigated outcomes amongst patients stable

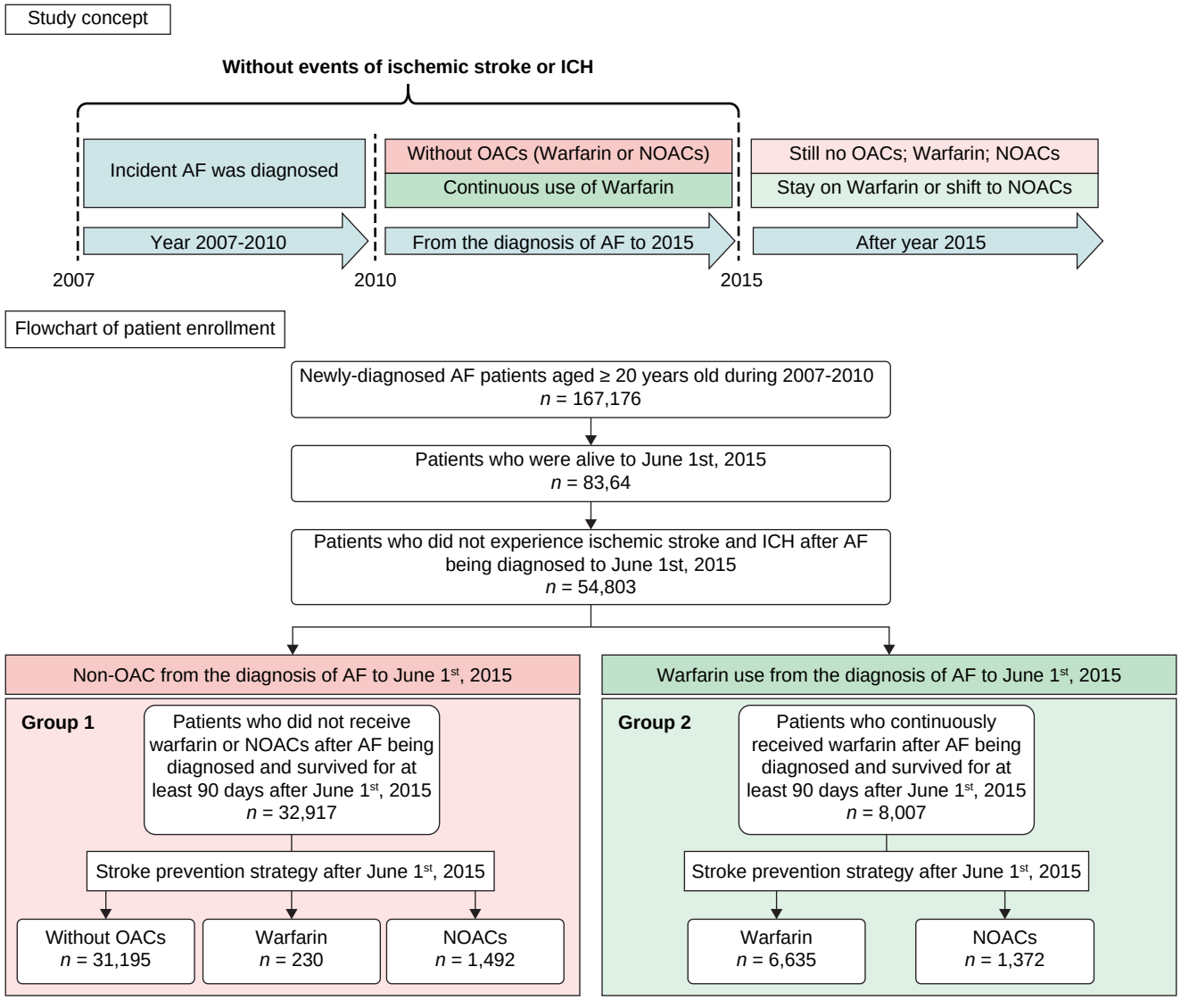


Figure 1 Study concept and the flowchart of the enrolment of the study population. AF = atrial fibrillation; ICH = intra-cranial haemorrhage; NOACs = non-vitamin K antagonist oral anticoagulants; OACs = oral anticoagulants.

on warfarin if they continued on their current regime, or if they were shifted to NOACs.

Methods

Database

This retrospective analysis used the 'National Health Insurance Research Database (NHIRD)' provided by the Health and Welfare Data Science Center (HWDC), Ministry of Health and Welfare (MOHW), Taiwan. The Taiwan National Health Insurance (NHI) system is a government-endorsed universal health insurance programme that offers comprehensive medical care coverage to all Taiwanese residents. All enrolees in this system were under the same rules for medical care coverage irrespective of their income levels which would minimize the potential disparate treatments owing to socioeconomic status. The NHIRD consists of detailed healthcare data from over 23 million enrolees, representing more than 99% of Taiwan's population. In this cohort dataset, the patients' original identification numbers have been encrypted to protect their privacy, but the encrypting procedure was consistent so that a linkage of the claims belonging to the same patient was feasible within the NHI database and can be followed continuously. The descriptions of Taiwan NHIRD have been reported in our previous studies.[4–10]

Study concept

The study concept of this study is summarized in *Figure 1*. We aimed to focus on incident AF patients who were non-anticoagulated or received warfarin and did not experience an ischaemic stroke or ICH for years. Then, we investigated the associations between the changes in stroke prevention strategies and the risks of clinical events after 1 June 2015 when NOACs were already available in Taiwan for several years (dabigatran was introduced in Taiwan in June 2012, rivaroxaban in February 2013 and apixaban in June 2014).

Study population

From 1 January 2007 to 31 December 2010, a total of 167 176 newly diagnosed AF patients aged ≥20 years were identified from the NHIRD. AF was diagnosed using the International Classification of Diseases (ICD), Ninth Revision, and Clinical Modification (ICD-9-CM) codes (427.31) registered by the physicians responsible for the treatments of patients. The diagnostic accuracy of AF using this definition in NHIRD has been validated previously.[11] Among these patients, 83 604 were alive until 1 June 2015, and 54 803 of them who did not experience an ischaemic stroke or intra-cranial haemorrhage (ICH) constituted the study population. The flowchart of patient enrolment is shown in *Figure 1*.

Group 1: original 'non-OAC' cohort from AF being diagnosed to 1 June 2015

Among the study population, 32 917 patients with a CHA_2DS_2-VASc score ≥1 for males or ≥2 for females who did not receive warfarin or NOACs and survived for at least 90 days after 1 June 2015 were defined as the 'original non-OAC cohort' (group 1). The median (interquartile range; IQR) durations from the diagnosis of AF to 1 June 2015 were 6.86 (5.53–8.07) years. These patients were then categorized into 3 groups according to the stroke prevention strategies they received after 1 June 2015; that is,

Table 1 Baseline characteristics in group 1 (AF patients who continued with no OACs and those who first started warfarin or NOACs)

Variables	Non-OACs *n* = 31 195	Warfarin *n* = 230	NOACs *n* = 1492	*P* value[a]	*P* value[b]	*P* value[c]
Age, years; mean value (SD)	73.59 (12.47)	72.00 (10.78)	76.76 (9.02)	<0.001	0.054	<0.001
Age ≥ 75 years, *n* (%)	15 723 (50.40)	103 (44.78)	920 (61.66)	<0.001	0.089	<0.001
Age 65–74 years, *n* (%)	8323 (26.68)	71 (30.87)	452 (30.29)	0.002	0.152	0.860
Male gender, *n* (%)	17 655 (56.60)	131 (56.96)	839 (56.23)	0.778	0.913	0.837
Comorbidities, *n* (%)						
Hypertension	26 151 (83.83)	192 (83.48)	1301 (87.20)	0.001	0.886	0.122
Diabetes mellitus	11 820 (37.89)	94 (40.87)	560 (37.53)	0.779	0.353	0.332
Congestive heart failure	12 301 (39.43)	128 (55.65)	757 (50.74)	0.000	<0.001	0.165
Vascular diseases	3378 (10.83)	20 (8.70)	172 (11.53)	0.396	0.300	0.204
COPD	8964 (28.74)	62 (26.96)	451 (30.23)	0.214	0.552	0.313
Hyperlipidemia	14 869 (47.66)	97 (42.17)	739 (49.53)	0.158	0.097	0.040
Autoimmune diseases	2077 (6.66)	19 (8.26)	92 (6.17)	0.458	0.333	0.229
Cancer	4010 (12.85)	25 (10.87)	197 (13.20)	0.693	0.371	0.395
Hyperthyroidism	1242 (3.98)	9 (3.91)	74 (4.96)	0.060	0.957	0.491
Abnormal renal function	6424 (20.59)	60 (26.09)	264 (17.69)	0.007	0.040	0.002
Abnormal liver function	7139 (22.89)	42 (18.26)	314 (21.05)	0.098	0.096	0.332
Anemia	5009 (16.06)	40 (17.39)	179 (12.00)	<0.001	0.584	0.022
History of bleeding	9573 (30.69)	65 (28.26)	457 (30.63)	0.961	0.426	0.467
Alcohol excess/abuse	744 (2.38)	2 (0.87)	25(1.68)	0.081	0.134	0.360
Gout	7320 (23.47)	52 (22.61)	357 (23.93)	0.682	0.759	0.662
CHA_2DS_2-VASc score; mean values (SD)	3.43 (1.43)	3.52 (1.41)	3.84 (1.27)	<0.001	0.342	<0.001
HAS-BLED score, mean value (SD)	2.84 (1.20)	2.70 (1.25)	2.69 (1.03)	<0.001	0.078	0.489

[a]*P* value between NOACs and non-OACs.
[b]*P* value between Warfarin and non-OACs.
[c]*P* value between NOACs and Warfarin.
COPD = chronic obstructive pulmonary disease; NOACs = non-vitamin K antagonist oral anticoagulants; SD = standard deviation

Table 2 Baseline characteristics of group 2 (AF patients continued on warfarin and those who shifted to NOACs)

Variables	Warfarin $n = 6635$	NOACs $n = 1372$	P value
Age, years; mean value (SD)	72.00 (10.78)	75.79 (9.59)	<0.001
Age ≥ 75 years, *n* (%)	2511 (37.84)	795 (57.94)	<0.001
Age 65–74 years, *n* (%)	2033 (30.64)	436 (31.78)	0.406
Male gender, *n* (%)	3683 (55.51)	814 (59.33)	<0.001
Comorbidities, *n* (%)			
Hypertension	5126 (77.26)	1207 (87.97)	<0.001
Diabetes mellitus	2333 (35.16)	557 (40.60)	<0.001
Congestive heart failure	4173 (62.89)	855 (62.32)	0.688
Vascular diseases	614 (9.25)	155 (11.30)	0.065
COPD	1787 (26.93)	456 (33.24)	<0.001
Hyperlipidemia	2889 (43.54)	687 (50.07)	<0.001
Autoimmune diseases	477 (7.19)	115 (8.38)	0.124
Cancer	703 (10.60)	198 (14.43)	<0.001
Hyperthyroidism	292 (4.40)	70 (5.10)	0.255
Abnormal renal function	1419 (21.39)	308 (22.45)	0.384
Abnormal liver function	1462 (22.03)	288 (20.99)	0.394
Anemia	1043 (15.72)	224 (16.33)	0.566
History of bleeding	2225 (33.53)	484 (35.28)	0.214
Alcohol excess/abuse	117 (1.76)	26 (1.90)	0.738
Gout	1794 (27.04)	376 (27.41)	0.781
CHA_2DS_2-VASc score; mean values (SD)	3.35 (1.41)	3.91 (1.31)	<0.001
HAS-BLED score, mean value (SD)	2.36 (1.24)	2.73 (1.07)	<0.001

COPD = chronic obstructive pulmonary disease; NOACs = non-vitamin K antagonist oral anticoagulants; SD = standard deviation.

without OACs ($n = 31\,195$), warfarin ($n = 230$), and NOACs ($n = 1492$). From group 1, we compared those who continued with no OAC with those who were first started on warfarin or those who first started on NOACs.

Group 2: original 'warfarin' cohort from AF being diagnosed to 1 June 2015

Among the study population, 8007 patients with a CHA_2DS_2-VASc score ≥1 for males or ≥2 for females who continuously received warfarin and survived for at least 90 days after 1 June 2015 were defined as the 'original warfarin cohort' (group 2). The median (interquartile range; IQR) durations from the diagnosis of AF to 1 June 2015 were 7.07 (5.70–8.19) years. These patients were then categorized into 2 groups according to the stroke prevention strategies they received after 1 June 2015; that is, staying on warfarin ($n = 6635$) and shifting to NOACs ($n = 1372$). From group 2, we compared those continuing on warfarin and those who shifted to NOACs.

Calculation of scores and definitions of clinical endpoints

The calculation rules of the CHA_2DS_2-VASc score, HAS-BLED score, and the definitions of clinical endpoints have been published in our previous works.[12,13] Notably, the component of 'labile international normalized ratio (INR)' was excluded from the calculation of the HAS-BLED score in the present study because the information about the INR of warfarin was not available in the Taiwan registry database. Also, abnormal renal and liver function were defined by the ICD-9-CM codes rather than laboratory data.

The clinical endpoints of this study included the occurrences of ischaemic stroke, ICH, major bleeding, all-cause mortality, composite events of ischaemic stroke or ICH, and ischaemic stroke or major bleeding. The accuracy of diagnosis of ischaemic stroke in Taiwan's NHIRD has been reported to be around 94.0%.[14] Another validation study also demonstrated that the diagnostic accuracy of ischaemic stroke in NHIRD was high, with a positive predictive value and sensitivity of 88.4% and 97.3%, respectively.[15] Major bleeding was defined as ICH or bleeding from the gastrointestinal or genitourinary or respiratory tract requiring hospitalization.

Falsification analysis (sensitivity analysis)

To further assess the likelihood of confounding by indication, we analysed three falsification endpoints that were unlikely to be affected by different stroke prevention strategies—urinary tract infection, cellulitis, and acute appendicitis. A finding of an association between different stroke prevention strategies and these falsification endpoints would therefore indicate the presence of unmeasured confounders. On the contrary, if the risks of these falsification endpoints of different patient groups did not differ significantly, the differences between different stroke prevention strategies concerning clinical outcomes in which we were interested may be less likely due to treatment selection bias.

Statistical analysis

Data were presented as the mean value and standard deviation (SD) for continuous variables, and proportions for categorical variables. Differences between continuous values and nominal variables were assessed using the unpaired two-tailed *t*-test and χ^2 test, respectively. The incidences of clinical events were calculated by dividing the number of events by person-time at risk. The risks of adverse events were assessed using the Cox regression analysis adjusted for variables that were significantly different between the comparison groups. All statistical significances were set at a $P < 0.05$.

Results

Table 1 summarizes the baseline characteristics in group 1, showing age differences between the subgroups, with the NOAC initiators being older and having a higher mean CHA_2DS_2-VASc score than the other two subgroups. *Table 2* summarizes the baseline characteristics of group 2. Those who shifted from warfarin to NOACs were older and had more comorbidities and higher mean CHA_2DS_2-VASc and HAS-BLED scores than those continuing on warfarin.

Outcomes in group 1

In group 1, compared to non-OAC (reference group), warfarin initiators showed no significant difference in ischaemic stroke [adjusted HR (aHR) 0.979, 95% confidence interval (CI) 0.863–1.110, $P = 0.137$] (*Figure 2*). Those initiated on NOACs were associated with a significantly lower risk of ischaemic stroke (aHR 0.867, 95% CI 0.786–0.956, $P = 0.043$). All-cause mortality was significantly lower in those initiated on warfarin (aHR 0.876, 95% CI 0.773–0.992, $P = 0.036$) or NOAC (aHR 0.798, 95% CI 0.644–0.989, $P = 0.047$). The composite of 'ischaemic stroke or major bleeding' was significantly lower in the warfarin (aHR 0.849, 95% CI 0.729–0.989, $P < 0.001$) or NOAC (aHR 0.789, 95% CI 0.682–0.913, $P < 0.001$) initiator subgroups.

In group 1 where the comparisons were confined to the subgroups started on warfarin and NOACs, the latter subgroup was associated with a significantly lower risk of ischaemic stroke (aHR 0.819, 95% CI 0.739–0.908, $P < 0.001$) with no significant differences in all-cause mortality, major bleeding or ICH (*Figure 3*). When compared to the warfarin subgroup, the composite of 'ischaemic stroke or ICH' and 'ischaemic stroke or major bleeding' was significantly lower in the NOAC initiator subgroup with an aHR of 0.927 (95% CI 0.865–0.994; $P = 0.042$) and 0.912 (95% CI 0.837–0.994; $P < 0.001$), respectively.

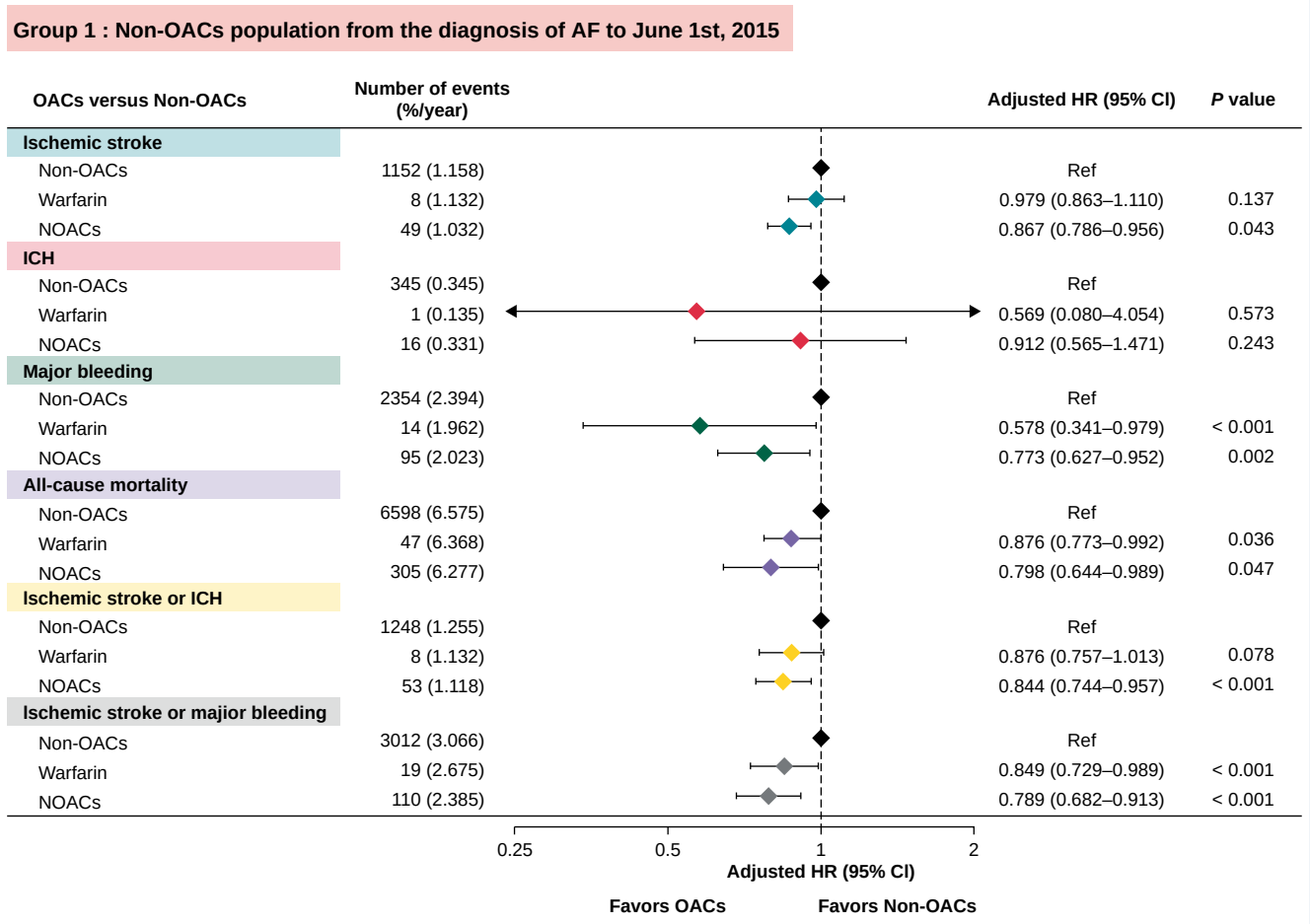


Figure 2 Risks of clinical events in different treatment groups among 'original non-OAC cohort'. AF = atrial fibrillation; CI = confidence interval; HR = hazard ratio; ICH = intra-cranial haemorrhage; NOACs = non-vitamin K antagonist oral anticoagulants; OACs = oral anticoagulants.

Outcomes in Group 2

In group 2, when compared to those who continued warfarin (reference group), those who shifted to NOACs were associated with a lower risk of ischaemic stroke (aHR 0.886, 95% CI 0.790–0.993, $P = 0.002$) and major bleeding (aHR 0.849, 95% CI 0.756–0.953, $P < 0.001$), with no significant differences in all-cause mortality and ICH (*Figure 4*). The composite outcomes of 'ischaemic stroke or major bleeding' or 'ischaemic stroke or ICH' were significantly lower in those shifted to NOACs.

Falsification analysis

In group 1, the risks of three falsification endpoints did not differ significantly between 'warfarin initiators and non-OAC' [aHR 1.174 (95% CI 0.838–1.646, $P = 0.351$) for urinary tract infection, aHR 1.490 (95% CI 0.923–2.402, $P = 0.487$) for cellulitis and aHR 1.422 (95% CI 0.20–10.178, $P = 0.726$) for acute appendicitis] or 'NOACs initiators and non-OAC' [aHR 1.031 (95% CI 0.894–1.189, $P = 0.675$) for urinary tract infection, aHR 0.969 (95% CI 0.787–1.193, $P = 0.660$) for cellulitis and aHR 1.073 (95% CI 0.437–2.637, $P = 0.878$) for acute appendicitis].

Similarly, in group 2, the risks of three falsification endpoints did not differ significantly between patients staying on warfarin or shifting to NOACs [aHR 1.041 (95% CI 0.887–1.223, $P = 0.624$) for urinary tract infection, aHR 0.864 (95% CI 0.682–1.094, $P = 0.226$) for cellulitis and aHR 0.325 (95% CI 0.077–1.373, $P = 0.126$) for acute appendicitis].

The results of the falsification analysis suggested that the significant differences between different treatment groups concerning clinical outcomes in which we were interested may be less likely due to treatment selection bias.

Discussion

This retrospective analysis from a nationwide cohort study provides novel 'real world' insights into contemporary practice on how AF patients who were previously well without taking any OACs would fare, if they continued untreated or if started on warfarin or NOAC. Also, amongst those who stayed well on warfarin for years, we show outcomes if they continued on their current regime, or if they were shifted to NOACs.

Our principal findings are as follows: (i) in patients with AF who were previously well without taking any OAC (group 1) for a median of nearly 7 years, those initiated on NOACs were associated with a significantly lower risk of ischaemic stroke whilst warfarin initiators showed no significant difference. Initiation of OAC (warfarin or NOAC) was associated with a lower risk of all-cause mortality, as well as the composite of 'ischaemic stroke or major bleeding'; (ii) In group 1, where the

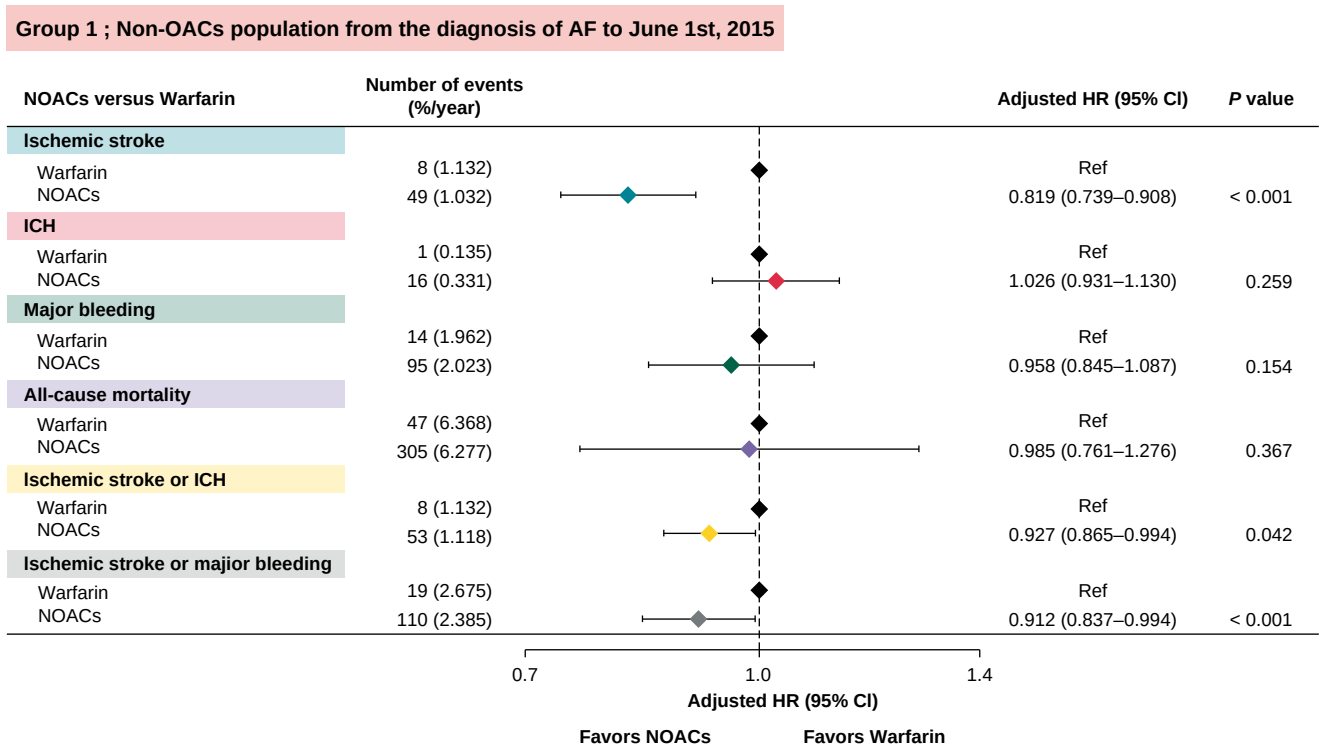


Figure 3 Risk of clinical events of NOACs compared to warfarin among 'original non-OAC cohort'. AF = atrial fibrillation; CI = confidence interval; HR = hazard ratio; ICH = intra-cranial haemorrhage; NOACs = non-vitamin K antagonist oral anticoagulants.

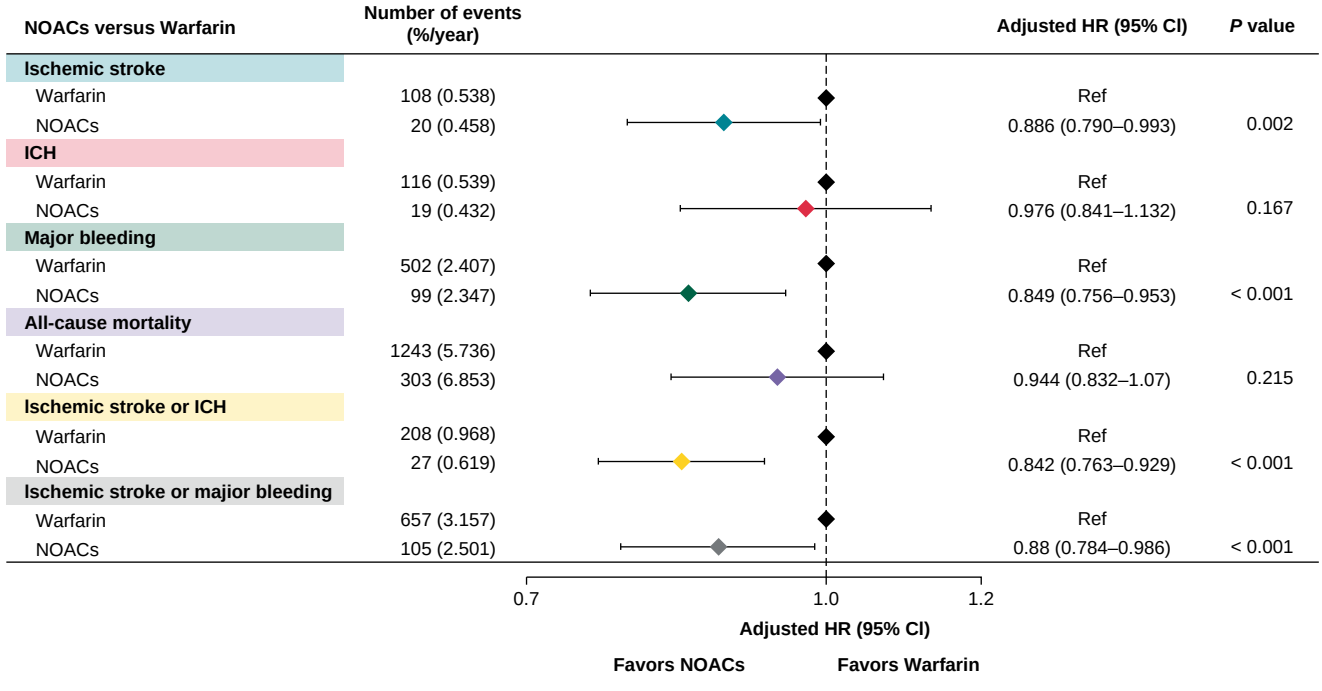


Figure 4 Risk of clinical events of NOACs compared to warfarin among 'original warfarin cohort'. AF = atrial fibrillation; CI = confidence interval; HR = hazard ratio; ICH = intra-cranial haemorrhage; NOACs = non-vitamin K antagonist oral anticoagulants.

comparisons were confined to the subgroups started on warfarin and NOACs, the latter was associated with a significantly lower risk of ischaemic stroke and the composite of 'ischaemic stroke or ICH' or 'ischaemic stroke or major bleeding' compared to those started on warfarin; and (iii) Even for patients stayed well on warfarin for a median of more than 7 years (group 2), those shifted to NOACs were associated with a lower risk of ischaemic stroke and major bleeding, as well as the composite outcomes of 'ischaemic stroke or major bleeding' or 'ischaemic stroke or ICH', compared to those continuing on warfarin.

We address a common clinical situation, as patients with AF who were previously well without taking any OACs for many years are frequently encountered, sometimes attending following AF screening or incidentally diagnosed when presenting to a healthcare professional for an incidental condition. Such patients would often ask if there was any value to start OAC since they have been 'survivors' free of any adverse events without OACs. We show those initiated on OAC were associated with a lower risk of all-cause mortality, as well as the composite of 'ischaemic stroke or major bleeding', while those initiated on NOACs were also associated with a lower risk of ischaemic stroke. Our data are supportive of the initiation of OAC, especially with a NOAC, in those AF patients who were previously well without taking any OACs for many years.

Interestingly, a lower risk of mortality despite a similar risk of ischaemic stroke was observed for patients who initiated warfarin. One possible explanation is that some of the causes of mortality for non-anticoagulated patients may be undiagnosed fatal stroke which could be prevented by the initiation of warfarin. Also, our results showed that the NOAC group was associated with a lower risk of major bleeding than the non-OAC group. Since our investigation was a retrospective analysis rather than a randomized trial, it is potentially possible that AF patients receiving NOACs were under more comprehensive medical care for close monitoring and corrections of modifiable bleeding risk factors which may lead to a better outcome.

On the other hand, we also commonly encounter AF patients who have stayed well on warfarin for years, and whether the warfarin should be shifted to NOACs is a clinically important issue. In the 2016 AF guidelines of the European Society of Cardiology (ESC), the recommendation was that when OAC is 'initiated' in a patient with AF who is eligible for a NOAC, a NOAC is recommended in preference to a VKA.[16] The latest 2020 ESC AF guidelines stated that NOACs are recommended in preference to vitamin K antagonists (VKA) for stroke prevention in AF patients who are 'eligible' for OAC, (class I recommendation).[1] This new recommendation may imply that NOACs should be chosen for stroke prevention not only limited to AF patients who 'initiated' OACs, but also for those who were previously treated with warfarin. However, the data behind this recommendation were very limited. Our results demonstrated that patients who were shifted from warfarin to NOACs did do better, with less ischaemic stroke and major bleeding, as well as the composite outcomes when compared to staying on warfarin. Therefore, even for patients who stayed well on warfarin for years, the shift from warfarin to NOACs should still be considered. It should be emphasized that the CHA_2DS_2-VASc scores of the NOAC groups were significantly higher than that of the warfarin and non-NOAC groups as shown in *Tables 1* and *2*. Despite this, the NOAC groups continuously demonstrated a lower risk of ischaemic stroke or major bleeding after the adjustment.

Study limitations

There are several limitations of this study mainly owing to the nature of the database we used. First, the diagnosis of AF and the occurrence of ischaemic stroke were based on the diagnostic codes registered by the physicians responsible for the treatments of patients; nonetheless, the accuracy of these diagnoses has been previously validated.[11,14,15] Second, information about the quality of anticoagulation control of warfarin in group 2, as reflected by the time in therapeutic range (TTR), was lacking in our dataset. We were not able to clarify whether patients shifted from warfarin to NOACs due to a suboptimal TTR, and therefore, the analyses would be in favour of NOACs. However, for patients in group 2, the median duration of warfarin use without any ischaemic stroke or ICH events was as long as 7 years, suggesting that these patients were staying well on warfarin. Furthermore, we cannot exclude the possibility that patients in group 1 who initiated warfarin and achieved a good TTR could have a lower risk of ischaemic stroke compared to non-OACs. Third, since our study was an observational study rather than a randomized trial, the presence of unmeasured confounders and selection bias is highly probable which could confound the analyses. However, for patients in group 2, the median duration of warfarin use without any ischaemic stroke or ICH events was as long as 7 years, suggesting that these patients were staying well on warfarin. may suggest that the significant differences between different treatment groups concerning clinical outcomes in which we were interested may be less likely due to treatment selection bias, we can only report 'associations' and do not imply causality. Fourth, we cannot completely exclude the possibility of type II error (false negative) in some of our analyses due to the relatively low event numbers. For example, in group 2, the risk of ICH did not differ significantly between NOAC and warfarin users which were different from our expectation. Beyond the possibility of type 2 error, another potential explanation is that we may have included AF patients that were well on warfarin without ICH for a long period (median 7.07 years), and therefore, the difference in ICH was not so evident. Finally, we analysed specific patients who survived and did not experience an ischaemic stroke or ICH from the diagnosis of AF to the year 2015, and we cannot exclude the possibility of potential survivorship bias in our investigation. However, we have to focus on this special population for our study purposes and to answer the questions we aimed to address.

Conclusions

In patients with AF who were previously well without taking any OAC, those initiated on NOACs were associated with a lower risk of ischaemic stroke and composite events. Even for AF patients under warfarin for years who did not experience ischaemic stroke and ICH, those shifted to NOACs were still associated with better clinical outcomes. Therefore, the use of NOACs should be considered for these patients.

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Conflict of interest: All authors have no conflict of interests.

Data availability

Data is available on request.

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