Original Contribution

Effectiveness and Safety of Non-Vitamin K Antagonist Oral Anticoagulants in Asian Patients With Atrial Fibrillation

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Background and Purpose—There are limited real-world data comparing the effectiveness and safety of non-vitamin K antagonist oral anticoagulants (NOACs) and warfarin in Asians with nonvalvular atrial fibrillation. We aimed to compare the effectiveness and safety between NOACs and warfarin users in the Korean atrial fibrillation population, with particular focus on high-risk patients.

Methods—Using the Korean National Health Insurance Service database, we analyzed the risk of ischemic stroke, intracranial hemorrhage (ICH) events, and all-cause death in NOAC users (n=11 611 total, n=5681 taking rivaroxaban, n=3741 taking dabigatran, and n=2189 taking apixaban) compared with propensity score-matched warfarin users (n=23 222) among patients with high-risk atrial fibrillation (CHA_2DS_2-VASc score ≥2) between 2014 and 2015.

Results—NOAC treatment was associated with similar risk of ischemic stroke and lower risk of ICH and all-cause mortality compared with warfarin. All 3 NOACs were associated with a similar risk of ischemic stroke and a lower risk of ICH compared with warfarin. Dabigatran and apixaban were associated with a lower risk of total mortality and the composite net clinical outcome (ischemic stroke, ICH, and all-cause death) compared with warfarin, whereas this was nonsignificant for rivaroxaban. Among previously oral anticoagulant–naive patients (n=23 262), dabigatran and apixaban were superior to warfarin for ICH prevention, whereas rivaroxaban and warfarin were associated with similar risk of ICH.

Conclusions—In real-world practice among a high-risk Asian atrial fibrillation population, all 3 NOACs demonstrated similar risk of ischemic stroke and lower risk of ICH compared with warfarin. All-cause mortality was significantly lower only with dabigatran and apixaban. **(*Stroke*. 2017;48:00-00. DOI: 10.1161/STROKEAHA.117.018773.)**

Key Words: anticoagulants ■ Asian continental ancestry group ■ atrial fibrillation ■ intracranial hemorrhages ■ stroke ■ warfarin

Since the introduction of non-vitamin K oral anticoagulants (NOACs) into daily practice, the global use of NOACs has been experiencing rapid growth.[1] After 4 major phase 3 trials, which have consistently shown comparable or better effectiveness and safety outcomes of NOACs compared with warfarin for stroke prevention in atrial fibrillation (AF),[2] recent real-world studies have reported the effectiveness and safety of NOACs in clinical practice.[1,3–5]

Asian patients with AF are known to have different characteristics compared with non-Asian patients with AF.[6] They are more prone to bleeding and less likely to achieve optimal international normalized ratio control during warfarin treatment. Also, Asian patients with AF taking warfarin are known to have higher rates of stroke/systemic embolism, ischemic stroke, and hemorrhagic stroke than non-Asians.[6]

More recently, real-word data on the use of NOACs have been reported and have been the subject of published systematic reviews and meta-analyses.[5,7] Given its later introduction and more limited healthcare reimbursement, fewer studies have specifically addressed the comparative effectiveness and safety of NOACs versus warfarin in the Asian population. In the Taiwanese nationwide cohort study, for example, most patients (≈90%) using low-dose NOACs showed favorable outcomes compared with the warfarin-treated population, despite having similar or lower $CHADS_2$ scores.[8]

This study aimed to compare the comparative risks of ischemic stroke, intracranial hemorrhage (ICH), and mortality associated with NOACs versus warfarin in the Korean AF population using a nationwide cohort. As secondary analyses, subgroup analyses on high-risk patients will be provided.

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Methods

Database

This study used records from the National Health Insurance Service (NHIS) database, which included patients' sociodemographic information, use of inpatient and outpatient services, and pharmacy dispensing claims. The majority (97.1%) of the total Korean population (≈50 million people) is covered by the mandatory NHIS. Diagnoses were classified using the *International Classification of Disease–Tenth Revision*, clinical modification codes. The NHIS database is open to all researchers whose study protocols have been approved by the official review committee. This study was exempt from review by the Seoul National University Hospital Institutional Review Board (E-1607-057-775).

Study Population

We identified nonvalvular AF patients with CHA_2DS_2-VASc score ≥2 who used anticoagulants from January 2014 to December 2015. In January 2013, 3 NOACs were simultaneously introduced to the Korean market for use in patients with nonvalvular AF. We excluded patients who had a history of thromboembolic event or ICH and only included patients taking anticoagulants for the primary prevention of stroke/systemic embolism. History of stroke, transient ischemic attack, and ICH were defined as having diagnostic codes for stroke, transient ischemic attack, and ICH within a 10-year period before 2014. We did this, as in those with previous diagnostic coding of stroke or ICH in the NHIS claims database, we could not differentiate whether patients had incident recurrent stroke or ICH because of similar diagnostic codes. To account for baseline differences and potential confounding effects, we used propensity score matching to select warfarin users corresponding to twice the number of NOAC users. The detailed enrolment criteria are shown in Figure 1.

Specific subgroups, that is, patients who were newly prescribed with oral anticoagulants (OAC) during the study period, patients with renal dysfunction, and the elderly (≥75 years old) were analyzed. To establish a cohort consisting of patients who were initially naive to OAC treatment, we excluded those who had previously used OAC in 2013. Additionally, NOAC users were classified as taking a regular dose (rivaroxaban 20 mg QD, dabigatran 150 mg BID, and apixaban 5 mg BID) or reduced dose (rivaroxaban 15/10 mg QD, dabigatran 110 mg BID, and apixaban 2.5 mg BID) and analyzed separately. Renal function was evaluated using test results obtained from standardized medical examinations, which are recommended to its customers (age, 40–79 years old) every 2 years. Among the study population, results were available in 11 742 (56.3%) patients in the warfarin group and 6533 (50.6%) in the NOAC group.

Variables and End-Point Definitions

We analyzed follow-up data for the occurrence of ischemic stroke (*International Classification of Disease–Tenth Revision* codes I63 or I64), ICH (*International Classification of Disease–Tenth Revision* codes I60-62), or all-cause death through December 2015. The composite net clinical outcome (ischemic stroke+all-cause death, ischemic stroke+ICH, or ischemic stroke+ICH+all-cause death) was also analyzed as a study outcome. Demographic and comorbidity data were obtained from the NHIS database. Detailed definitions of all variables and *International Classification of Disease–Tenth Revision* codes are described in Table I in the online-only Data Supplement.

Statistical Analysis

We used time-to-event analysis to compare the risk of an outcome between treatment groups, measuring risk time from initial prescription to the relevant event, emigration, death, or end of follow-up,

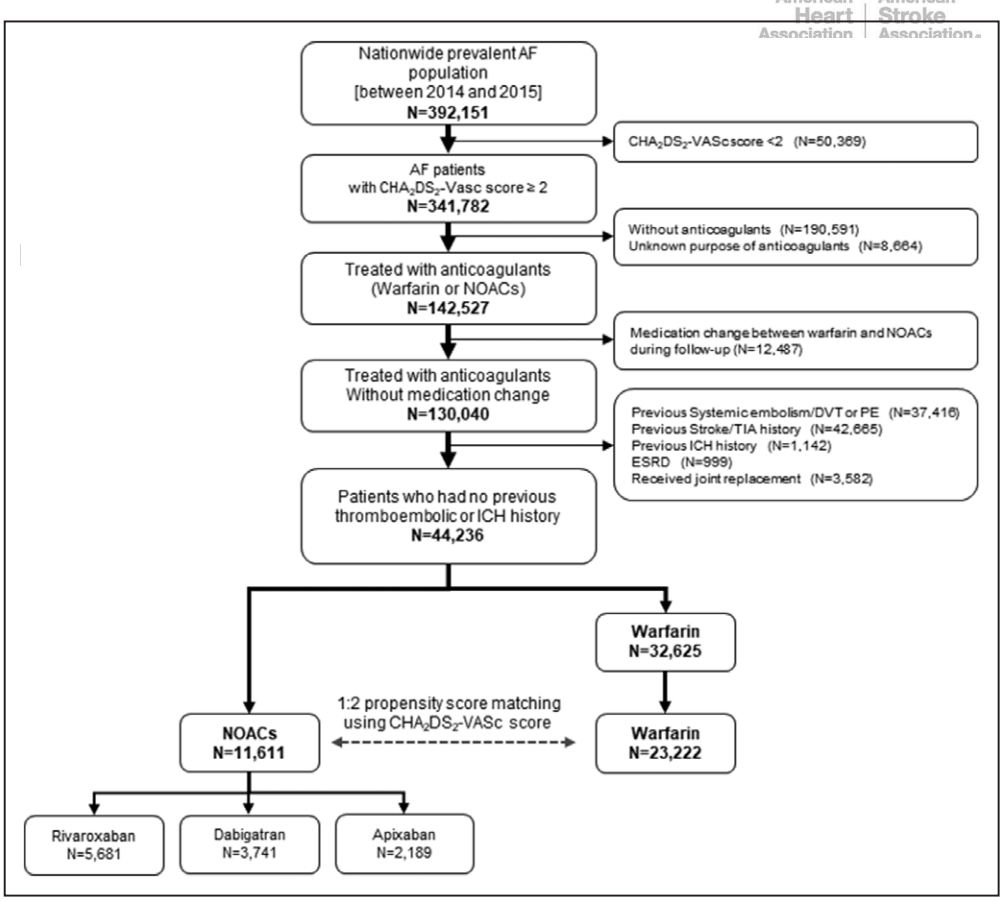

Figure 1. Patient enrolment flow. AF indicates atrial fibrillation; DVT, deep vein thrombosis; ESRD, end-stage renal disease; ICH, intracranial hemorrhage; NOAC, non-vitamin K antagonist oral anticoagulant; and PE, pulmonary embolism.

whichever came first. An intention to treat approach was applied for the analyses of all end points.

We calculated crude incidence as the number of events divided by 100 person-years (percentage/years). One to 2 propensity score-matched analyses (matched with CHA_2Ds_2-VASc score) were performed between the NOAC and warfarin groups. Cox regression was used to compare event rates between treatment groups, with warfarin as the primary reference. All hazard ratios (HRs) were adjusted according to CHA_2DS_2-VASc score. Subgroup analyses were performed in patient groups according to age, sex, CHA_2DS_2-VASc score, renal function, whether a regular or reduced dose of NOACs was used, and whether patients initially started anticoagulant therapy during the study period.

All statistical analyses were performed using SAS, version 9.3 (SAS Institute, Cary, NC).

Results

We identified 44 236 patients with AF as OAC users between 2014 and 2015, including 11 611 patients receiving 1 of the 3 NOACs (rivaroxaban, dabigatran, or apixaban) without previous thromboembolic or ICH history. The study population (n=44 236) was categorized according to treatment type: warfarin (n=32 625; 73.8%), rivaroxaban (n=5681; 12.8%), dabigatran (n=3741; 8.5%), and apixaban (n=2189; 4.9%). With propensity score matching, a total of 23 222 warfarin users were selected for the study analysis. Patient enrolment and flow are shown in Figure 1.

Table 1 shows the demographic characteristics of enrolled patients. The average follow-up was 1.2 years, with the shortest in the apixaban group (average 0.4 years) and the longest in the warfarin group (average 1.5 years). Before propensity score matching, the warfarin group had a lower average CHA_2DS_2-VASc score (3.43) than the NOAC group (3.57), but after propensity score matching, the average CHA_2DS_2-VASc score of the warfarin group was 3.57±1.31. Among NOACs users, rivaroxaban users had the highest average CHA_2DS_2-VASc score (3.60) and dabigatran users had the lowest (3.51). The baseline characteristics of the overall population and regular/reduced-dose NOAC users are summarized in Table II in the online-only Data Supplement. About 53% of NOAC users were prescribed a reduced dose of NOAC. Reduced doses were prescribed in 2852 (50.2%) of rivaroxaban group, in 2345 (62.6%) of dabigatran group, and in 923 (42.2%) of apixaban group.

Ischemic Stroke

During the 2-year follow-up, there were 813 ischemic stroke events, and 352 events (43.3%) occurred within the first 6 months. NOACs demonstrated a nonsignificant difference in the rate of ischemic stroke compared with warfarin (HR for NOAC, 0.98; 95% confidence interval [CI], 0.78–1.22; Figure 2A). All 3 NOACs showed similar ischemic stroke rates in comparison with warfarin (rivaroxaban 1.9%, dabigatran 1.8%, apixaban 1.3%, and warfarin 1.5% per year). Overall crude cumulative incidence curves for ischemic stroke showed no significant differences among the 4 treatment groups (Figure 3A). Detailed data for number of events and incidence rates according to treatment are summarized in Table 2.

In subgroup analysis, NOACs were associated with lower risk of ischemic stroke than warfarin, especially in patients <65 years of age (Figure 4). Notwithstanding the smaller numbers and modest follow-up, reduced-dose NOAC users demonstrated nonsignificant difference in risk of ischemic stroke to regular-dose users in comparison with warfarin users. The

Table 1. Baseline Characteristics According to Treatment

Characteristics	Total	NOAC				Warfarin
		Rivaroxaban	Dabigatran	Apixaban	All	
No. in group	34 833	5681	3741	2189	11 611	23 222
Women	15 289 (43.9%)	2686 (47.3%)	1570 (42.0%)	998 (45.6%)	5254 (45.3%)	10 035 (43.1%)
Age, y	69.26±10.76	70.5±9.9	69.3±10.0	70.3±10.0	70.1±9.9	68.82±11.1
≥65	25 166 (72.3%)	4418 (77.8%)	2732 (73.0%)	1671 (76.3%)	8821 (76.0%)	16 345 (70.4%)
≥75	11 873 (34.1%)	2029 (35.7%)	1215 (32.5%)	801 (36.6%)	4045 (34.8%)	7828 (33.7%)
CHA_2DS_2-VASc score	3.57±1.31	3.60±1.32	3.51±1.28	3.57±1.29	3.57±1.31	3.57±1.31
2	8775 (25.2%)	1394 (24.5%)	993 (26.5%)	538 (24.6%)	2925 (25.2%)	5850 (25.2%)
3	9684 (27.8%)	1556 (27.4%)	1060 (28.3%)	612 (28.0%)	3228 (27.8%)	6456 (27.8%)
4	8061 (23.1%)	1310 (23.1%)	854 (22.8%)	523 (23.9%)	2687 (23.1%)	5374 (23.1%)
≥5	8313 (23.9%)	1421 (25.0%)	834 (22.3%)	516 (23.6%)	2771 (23.9%)	5542 (23.9%)
Hypertension	26 712 (76.7%)	4298 (75.7%)	2872 (76.8%)	1683 (76.9%)	8853 (76.3%)	17 859 (76.9%)
Diabetes mellitus	8914 (25.6%)	1353 (23.8%)	990 (26.5%)	517 (23.6%)	2860 (24.6%)	6054 (26.1%)
Dyslipidemia	14 690 (42.2%)	2456 (43.2%)	1719 (46.0%)	993 (45.4%)	5168 (44.5%)	9522 (41.0%)
Heart failure	17 052 (49.0%)	2519 (44.3%)	1682 (45.0%)	942 (43.0%)	5143 (44.3%)	11 909 (51.3%)
Myocardial infarction	1715 (4.9%)	243 (4.3%)	161 (4.3%)	115 (5.3%)	519 (4.5%)	1196 (5.2%)
Chronic obstructive pulmonary disease	7306 (21.0%)	1228 (21.6%)	751 (20.1%)	473 (21.6%)	2452 (21.1%)	4854 (20.9%)
Peripheral artery disease	5009 (14.4%)	945 (16.6%)	650 (17.4%)	335 (15.3%)	1930 (16.6%)	3079 (13.3%)
Follow-up, y	1.17±0.72	0.50±0.51	0.55±0.57	0.40±0.39	0.50±0.51	1.51±0.56

NOAC indicates non-vitamin K antagonist oral anticoagulants.

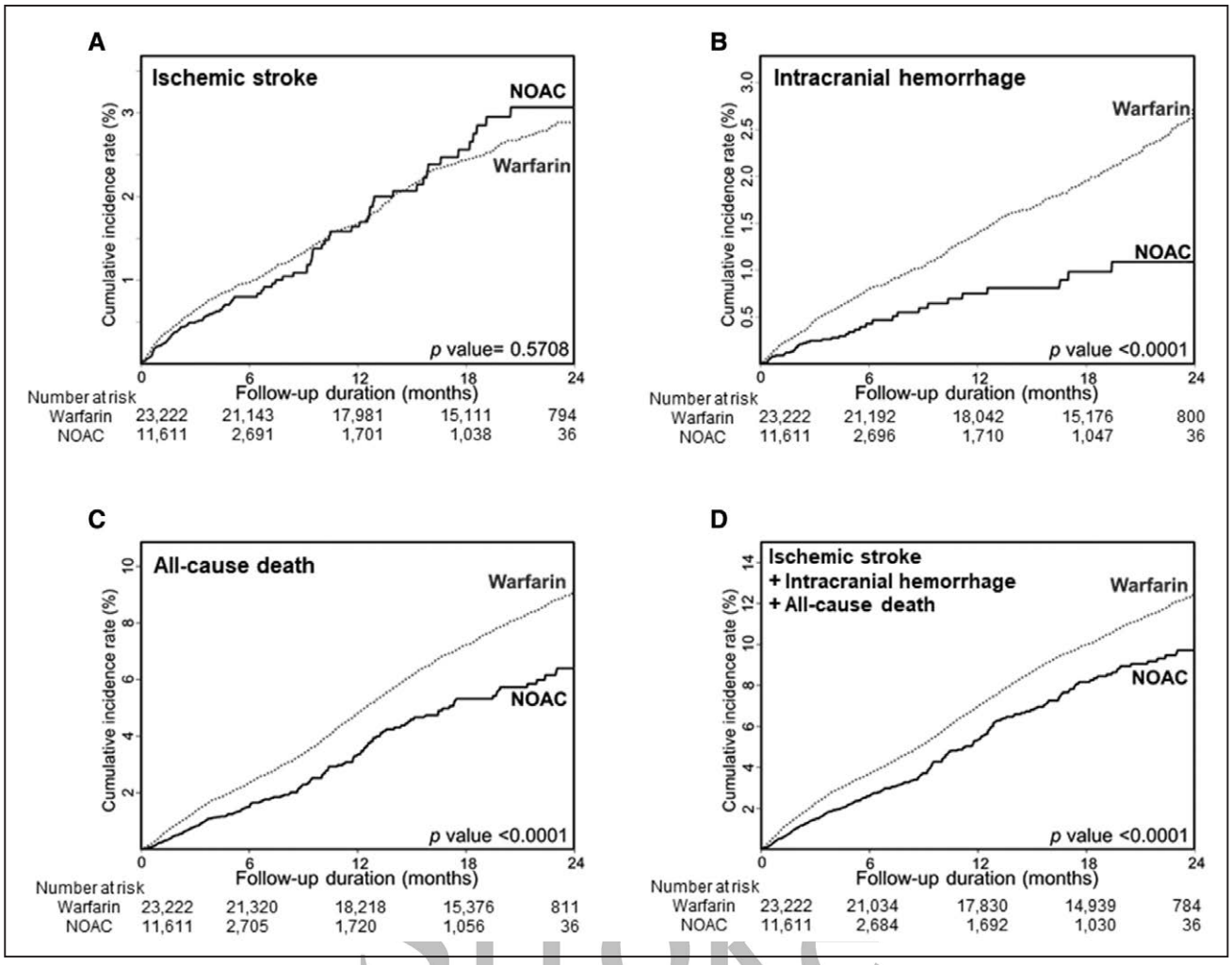

Figure 2. Crude cumulative incidence curves of ischemic stroke, intracranial hemorrhage, all-cause mortality, and combined outcome according to initiated treatment (warfarin vs non-vitamin K antagonist oral anticoagulant [NOAC]).

results of interaction analysis are described in Table III in the online-only Data Supplement.

Intracranial Hemorrhage

During the 2-year follow-up, there were 672 ICH events, and 273 events (40.6%) occurred within the first 6 months. Patients taking a NOAC had significantly lower ICH incidence compared with those taking warfarin (0.7% versus 1.3% per year; HR for NOAC, 0.50; 95% CI, 0.36–0.68; Figure 2B). All 3 NOACs were associated with lower ICH event rates than warfarin (rivaroxaban 0.9%, dabigatran 0.6%, apixaban 0.5%, and warfarin 1.3% per year). Overall crude cumulative incidence curves revealed lower ICH incidence in all NOAC users and each individual NOAC group compared with the warfarin group (Figure 3B).

The safety of NOACs in relation to ICH was significantly superior to warfarin regardless of sex, age, CHA_2DS_2-VASc score, or dose reduction (Figure 4). When comparing each NOAC with warfarin, there was no significant difference between warfarin and rivaroxaban in women, patients <65 years, or those with a CHA_2DS_2-VASc score of 2 points. Dabigatran did not significantly differ from warfarin in women or patients with a CHA_2DS_2-VASc score of 2, and finally, apixaban was not significantly different from warfarin in women and patients <65 years of age.

All-Cause Death

During the 2-year follow-up, there were 2450 deaths, and 818 events (33.4%) occurred within first 6 months. NOAC users had a significantly lower all-cause mortality rate than warfarin users (HR for NOAC, 0.70; 95% CI, 0.59–0.81; Figure 2C). Patients taking dabigatran and apixaban had lower mortality rates than warfarin users, whereas mortality on rivaroxaban was nonsignificant compared with warfarin (rivaroxaban 4.5%, dabigatran 2.4%, apixaban 1.5%, and warfarin 4.6% per year; Figure 3C).

In the subgroup analysis, NOAC was associated with a better outcome than warfarin regardless of dose reduction (Figure 4). The mortality benefit of dabigatran and apixaban was most marked in men, patients ≥65 years of age, and those with a CHA_2DS_2-VASc score >2.

Composite Net Clinical Outcome

NOAC users demonstrated a better outcome than warfarin users in all 3 composite end points of ischemic stroke+ICH (HR for NOAC, 0.79; 95% CI, 0.65–0.94), ischemic stroke+all-cause

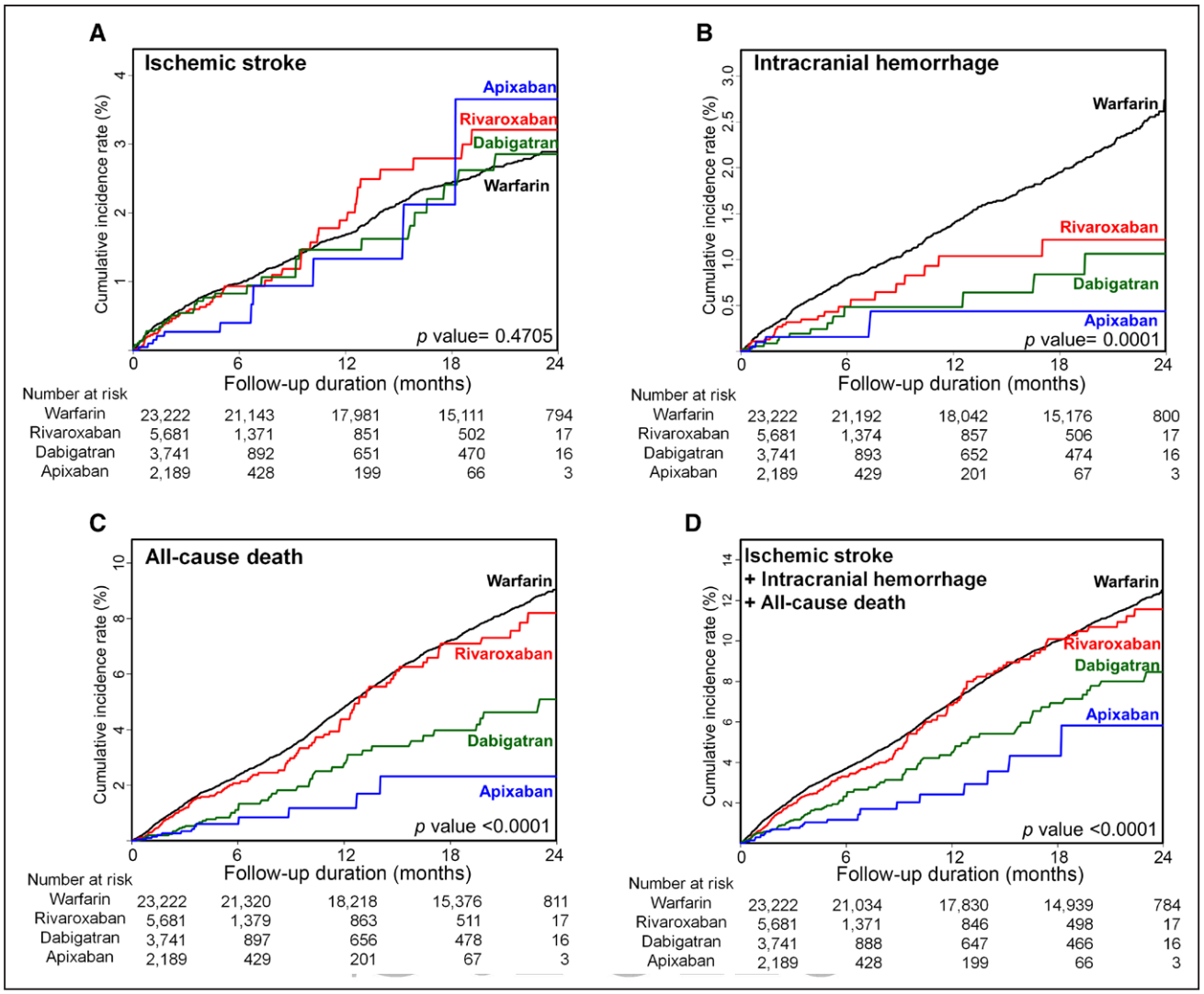

Figure 3. Crude cumulative incidence curves of ischemic stroke, intracranial hemorrhage, all-cause mortality, and combined outcome according to initiated treatment (warfarin vs each non-vitamin K antagonist oral anticoagulant).

death (HR for NOAC, 0.78; 95% CI, 0.68–0.89), and ischemic stroke+ICH+all-cause death (HR for NOAC, 0.76; 95% CI, 0.67–0.86; Figure 2D; Figure I in the online-only Data Supplement).

Apixaban was associated with significantly lower risk of all 3 composite end points compared with warfarin, whereas dabigatran was associated with significantly lower risk of ischemic stroke+all-cause death and ischemic stroke+ICH+all-cause death. Rivaroxaban was nonsignificantly different from warfarin for all 3 composite end points (Figure 3D; Figure II in the online-only Data Supplement).

The effectiveness and safety of NOACs in relation to combined outcomes were superior to warfarin regardless of sex, age, CHA_2DS_2-VASc score, or dose reduction (Figure II in the online-only Data Supplement). The benefit of NOAC was most marked in dabigatran and apixaban.

Subgroup Analyses

New Starters on Oral Anticoagulants

After excluding patients who had taken anticoagulants in 2013, we analyzed 23 262 OAC-naive patients with AF (5116 rivaroxaban, 3168 dabigatran, 2066 apixaban, and 12 912 warfarin users; Table IV in the online-only Data Supplement; Figure III in the online-only Data Supplement). Figure IV in the online-only Data Supplement shows the sharp increase in new NOAC users in July 2015, which occurred following expanded reimbursement coverage. CHA_2DS_2-VASc scores were similar between warfarin and NOAC new users (Table V in the online-only Data Supplement).

All NOAC users showed comparable outcomes to warfarin for ischemic stroke (HR for NOAC, 0.86; 95% CI, 0.65–1.13). Dabigatran and apixaban were superior to warfarin for ICH prevention (HR for dabigatran, 0.43; 95% CI, 0.19–0.82 and HR for apixaban, 0.32; 95% CI, 0.10–0.78), and rivaroxaban was nonsignificantly different to warfarin (HR for rivaroxaban, 0.71; 95% CI, 0.44–1.08). NOAC use was associated with mortality reduction compared with warfarin (HR for NOACs, 0.55; 95% CI, 0.45–0.67), as well as for all composite outcomes (Figure V in the online-only Data Supplement).

Table 2. Number of Events, and Crude and Matched Event Rates According to Treatment During Overall Follow-Up

	No. of Patients	Ischemic Stroke		ICH		All-Cause Death		Stroke+Death		Stroke+ICH		Stroke+ICH+Death	
		Events	IR*	Events	IR	Events	IR	Events	IR	Events	IR	Events	IR
NOAC	11 611	102	1.78	43	0.75	189	3.27	280	4.88	139	2.42	315	5.50
Rivaroxaban	5681	55	1.95	26	0.92	127	4.46	174	6.16	77	2.73	196	6.96
Dabigatran	3741	36	1.77	13	0.64	49	2.39	83	4.08	48	2.36	93	4.58
Apixaban	2189	11	1.25	4	0.45	13	1.47	23	2.62	14	1.59	26	2.96
Regular dose NOAC	5491	49	1.74	15	0.53	57	2.02	102	3.63	61	2.18	114	4.08
Reduced dose NOAC	6120	53	1.80	28	0.95	132	4.46	178	6.05	78	2.66	201	6.86
Warfarin													
PS matched patients	23 222	545	1.57	468	1.34	1699	4.84	2096	6.04	931	2.70	2359	6.85
Overall patients	32 625	711	1.45	629	1.28	2261	4.57	2780	5.68	1231	2.53	3142	6.46

ICH indicates intracranial hemorrhage; IR, incidence rate; NOAC, non-vitamin K antagonist oral anticoagulants; and PS, propensity score.
*Events divided by 100 person-years (%/y).

Elderly Patients (≥75 Years Old)

Among 14 164 (32% of the total) patients with age ≥75 (10 119 warfarin users and 4045 NOAC users), there were 383 (47.1%) stroke events, 292 (43.5%) ICH events, and 1539 (62.8%) deaths. In this group, NOAC users showed comparable outcomes to warfarin users for ischemic stroke (HR for NOAC, 1.1; 95% CI, 0.80–1.49). ICH event rates were lower in the overall NOAC users compared with warfarin users (HR for NOAC, 0.63; 95% CI, 0.40–0.95), although each NOAC did not have statistical difference with warfarin. Also, NOAC users showed lower mortality than warfarin (HR for NOAC, 0.72; 95% CI, 0.59–0.86).

Dabigatran and apixaban showed lower mortality rates than warfarin, whereas rivaroxaban had no significant difference with warfarin. Elderly NOAC users also demonstrated comparable or better outcomes than warfarin users in all 3 composite end points of ischemic stroke+ICH (HR for NOAC, 0.90; 95% CI, 0.69–1.16), ischemic stroke+all-cause death (HR for NOAC, 0.82; 95% CI, 0.69–0.96), and ischemic stroke+ICH+all-cause death (HR for NOAC, 0.81; 95% CI, 0.69–0.95; Figure VI in the online-only Data Supplement).

Patients With Renal Dysfunction

We further analyzed 18 275 patients whose renal function data were available. There were 16 956 (92.8%) patients with glomerular filtration rate ≥50 mL/min and 1319 (7.2%) patients with glomerular filtration rate <50 mL/min. In patients with glomerular filtration rate <50 mL/min, there were 37 (12.8%) stroke events, 21 (9.5%) ICH events, and 47 (17.8%) mortality events. NOAC users showed results comparable with warfarin users in stroke (HR for NOAC, 0.69; 95% CI, 0.11–2.41), ICH (HR for NOAC, 0.59; 95% CI, 0.03–2.99) and mortality (HR for NOAC, 1.73; 95% CI, 0.58–4.19; Figure VII in the online-only Data Supplement).

Discussion

To the best of our knowledge, this is the largest Asian study to report real-world safety and effectiveness data for all 3 NOACs (dabigatran, rivaroxaban, and apixaban) in comparison with warfarin. In this large population-based cohort study, we found that (1) NOACs demonstrated comparable effectiveness but better safety, mortality, and combined end points compared with warfarin; (2) all 3 NOACs were associated with no significant difference in risk of ischemic stroke but lower risk of ICH compared with warfarin; (3) dabigatran and apixaban were associated with lower mortality than warfarin, whereas rivaroxaban was not; (4) dabigatran and apixaban were associated with lower risk for combined end points than warfarin, whereas rivaroxaban was nonsignificantly different; (5) in OAC-naive patients, dabigatran and apixaban showed lower risk of ICH, whereas rivaroxaban did not; and (6) in high-risk patients, especially those aged ≥75, NOACs demonstrated lower risk of ICH compared with warfarin.

We observed differential prescribing patterns of OACs in relation to patient characteristics. For example, before propensity score matching, the average CHA_2DS_2-VASc score of patients with NOAC was higher than that of patients prescribed warfarin. Because of the regulations in Korea, NOACs can be reimbursed only in patients with a CHA_2DS_2-VASc score ≥2 points or who experience warfarin-related complications or labile international normalized ratio control. Although the average CHA_2DS_2-VASc score was similar between the NOAC and warfarin groups after propensity score-matching, there were still different characteristics among 3 NOACs. For example, rivaroxaban was prescribed for the patients with highest average CHA_2DS_2-VASc score, whereas dabigatran was preferentially prescribed for younger patients and was associated with the lowest stroke risk. Various different baseline characteristics among the 3 NOAC groups could have an impact on the outcomes observed in this study.

Comparison of Asian and Non-Asian Real-World Data

Asian patients with non-valvular AF have different characteristics compared with non-Asian patients in recent phase 3 trials

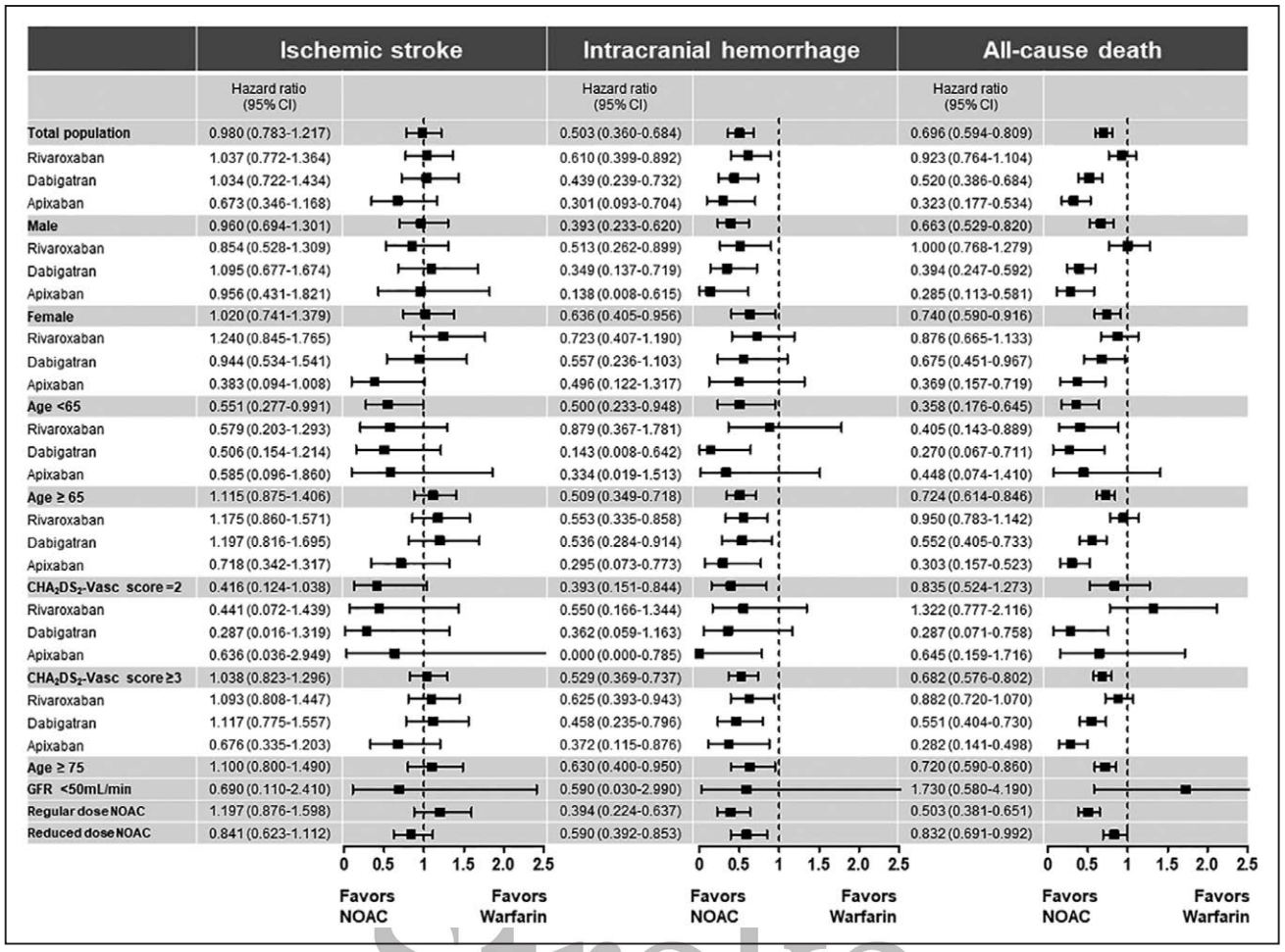

Figure 4. Cox hazard ratios for overall follow-up for non-vitamin K antagonist oral anticoagulants (NOACs) vs warfarin for ischemic stroke, intracranial hemorrhage, and all-cause death. CI indicates confidence interval.

and higher rates of stroke and major bleeding, including ICH.[9] In recent reports of real-world data on the effectiveness and safety of NOACs in comparison with warfarin, NOACs demonstrated comparable results with regard to stroke prevention, with better safety outcomes.[4,5,7] However, most prior real-world studies have reported on non-Asian populations. Previous studies in Asians revealed that NOACs were more frequently prescribed at a reduced dose compared with non-Asian patients. In claims data from Taiwan, for example, 87% of all enrolled NOAC users were taking a reduced dose of NOAC, and this prescription pattern was presumed to reflect the lower body mass index of the Taiwanese population, physicians' prescribing habits, and predominantly older population with comorbidities because of insurance policy and high ICH risk in Asian populations.[10] In Japan, reduced-dose rivaroxaban (15/10 mg QD for creatinine clearance 30–49 mL/min) was approved dose for stroke prevention in patients with AF on the basis of the J-ROCKET AF study (Japanese Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation).[11]

The prescription rates of reduced-dose NOAC are typically 10% to 20% in data from the United States,[12] 59% in a French nationwide cohort,[13] and 49% in a Danish cohort.[1] The rate of reduced-dose NOAC prescription in our study was 53%, which is broadly similar to European real-world data. The high use of reduced-dose NOAC could be explained as follows: first, the average body weight of men and women in Korea aged ≥40 is 67.3 (body mass index, 24.2) and 57.8 kg (body mass index, 23.8), respectively, and ≈25% of men and 50% of women weigh <60 kg.[14] Recently, we reported that being underweight was associated with an increased risk of major bleeding and all-cause death compared with being normal weight or overweight to obese, whereas the risk of thromboembolism did not significantly differ across weight groups.[15] Indeed, this difference in body weight between Asians and non-Asians could be one reason why Asian patients with nonvalvular AF were more frequently prescribed a reduced dose of NOAC. Second, NOAC prescriptions in the current Korean insurance system are mainly limited to patients with a CHA_2DS_2-VASc score ≥2 points. Patients who are indicated for NOACs are likely to have more comorbidities, such as decreased renal function, and, therefore, physicians may be concerned about the risk of bleeding and consequently prescribe the reduced dose. Third, given the high incidence of ICH in Asian patients with AF, physicians may adopt more cautious prescribing habits. Nevertheless, NOACs overall demonstrated comparable effectiveness and superior safety to warfarin in our study.

Many reports of real-world data have provided favorable evidence for the effectiveness and safety of NOACs compared with warfarin. Fewer reports have been published from Asian countries.[10,16] One reason may be the delayed entry of NOAC drugs in Asian markets, also leading to a limited prognostic observation period. Also, there are few Asian countries with well-established national compulsory insurance systems, with billing data distributed at the national level. Despite the inherent limitations of using claim data, the present study specifically focuses on short-term outcomes of ischemic stroke because NOACs appeared in the Korean market in 2013, and reimbursement criteria were only expanded in July 2015. Based on the release of NHIS data for 2016, the average follow-up duration of all patients taking OACs was ≈6 months. Nonetheless, a major strength of this study is the avoidance of selection bias by analyzing the insurance data of the whole Korean population. Early thromboembolic events are known to have a major impact on the overall success of treatment in patients with AF, which is closely related to the persistence of long-term treatment.[17] In our study, ischemic stroke risk was similar between NOAC and warfarin users. In the sensitivity analysis, neither NOAC dose nor patient characteristics affected this trend.

OACs are known to reduce the risk of both stroke and death; therefore, we included all-cause mortality as a single end point and as a combined end point with stroke.[18] In our analysis, mortality risk was similar between warfarin and rivaroxaban users and significantly lower among apixaban or dabigatran users. The composite net clinical outcome ischemic stroke+all-cause death was also highest in the warfarin group, and only dabigatran and apixaban showed superiority to warfarin for the composite effectiveness outcomes. The higher average CHA_2DS_2-VASc scores in rivaroxaban users could reflect the greater disease severity of this group compared with other NOAC groups, which might explain their higher mortality We focused on ICH events in this study because ICH is responsible for most of the death and disability attributable to anticoagulant-associated bleeding.[19] ICH in the anticoagulated population occurs at a rate of 0.2% to 1.0% per year[20] and is reduced by using NOACs instead of warfarin.[21,22] In our study, all doses of NOACs, even regular-dose rivaroxaban, demonstrated a safety benefit compared with warfarin.

Although elderly patients with AF have a higher risk of bleeding, the benefits of warfarin therapy outweigh bleeding risk regardless of increasing age.[23] In our subgroup analysis of elderly population, NOAC showed similar results in stroke prevention but lower risk of ICH and mortality compared with warfarin. In those with renal dysfunction, NOAC showed broadly similar effectiveness and safety compared with warfarin. Although the high-risk subgroup analysis was available in only a half of total population, given the large numbers in the database, this should not markedly affect the results.

Limitations

This study had several limitations. First, the NHIS data do not contain laboratory or clinical measurements. Therefore, important information was not available for analysis, including serum hemoglobin, renal and liver function, international normalized ratio, blood pressure, body weight, and height. Therefore, we could not analyze the quality of anticoagulation control among warfarin users, as reflected by time in therapeutic range, which is important for warfarin management.[24] Although not covered in this study, the GARFIELD registry (Global Anticoagulant Registry in the FIELD-Atrial Fibrillation) in which a large number of Korean patients are enrolled showed that the therapeutic range of international normalized ratio is lower in Korean than in other regions.[25] Also, we could not calculate HAS-BLED scores because of limited information about laboratory data. Second, our analyses were not focused on direct comparisons of one NOAC agent against another; further research is warranted to establish the comparative effectiveness and safety across different NOAC agents. Third, medication adherence and persistence data are lacking in this study. Patients prescribed with warfarin have difficulties in maintaining adequate adherence.[26] Also, one third of patients with AF discontinued warfarin, despite the obvious benefit of stroke prevention.[27] Indeed, NOACs have been reported to have variable adherence and persistence.[28,29] All these factors might have influenced the outcomes of each group of patients. Finally, we excluded the patients with a history of ischemic stroke or ICH; therefore, patients indicated for secondary stroke prevention were not included in this analysis. These might be some of the reasons of lower annual incidence of ischemic stroke and ICH in this study compared with Asian stroke and ICH rates reported in the major phase 3 clinical trials.[9] In a previous study, NOACs showed some differences in effectiveness and bleeding between primary and secondary prevention.[30]

Conclusions

In real-world practice among a high-risk Asian AF population, all 3 NOACs demonstrated similar risk of ischemic stroke and lower risk of ICH compared with warfarin. All-cause mortality was significantly lower only with dabigatran and apixaban.

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Disclosures

Dr Lip is a consultant for Bayer/Janssen, Bristol-Myers Squibb/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife, and Daiichi Sankyo; speaker for Bayer, Bristol-Myers Squibb/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche, and Daiichi Sankyo. No fees are received personally. The other authors report no conflicts.

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Effectiveness and Safety of Non-Vitamin K Antagonist Oral Anticoagulants in Asian Patients With Atrial Fibrillation

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SUPPLEMENTAL MATERIAL

Supplementary table I. Definition of each variable using ICD-10 codes

Disease	ICD-10 Codes	Diagnostic definition
Atrial fibrillation	Inclusion: I480, I481, I482, I483, I484, I489 Exclusion: I050, I052, I059, Z952-Z954	Admission or outpatient department ≥2
Ischemic stroke	I63, I64	Admission and brain imaging (CT or MRI)
Intracranial hemorrhage	I60-62	Admission ≥1 or RBC transfusion ≥1
Hypertension	I10-13, I15	Admission or outpatient department ≥2
Diabetes mellitus	E11-14	(Admission or outpatient department ≥2) and use of anti-diabetic medication
Dyslipidemia	E78	Admission or outpatient department ≥1
Ischemic heart disease	I20-25	Admission or outpatient department ≥2
Prior myocardial infarction	I21-22	Admission or outpatient department ≥1
Congestive heart failure	I63,64	Admission or outpatient department ≥1
Peripheral arterial disease	I70, I73	Admission or outpatient department ≥2
Systemic arterial thromboembolism	I74	Admission ≥1
Venous thromboembolism	I26, I802	Admission ≥1
End stage renal disease	N185, Z49	Dialysis ≥2
Received joint replacement	N0711, N1711, N1721, N2070, N3710,N3721, N3717, N3720, N2072, N2077, N3722, N3727	Admission ≥1
Pulmonary thromboembolism	I26	Admission ≥1

Supplementary table II. Baseline characteristics of warfarin and NOAC users according to prescribed dose (regular versus reduced dose)

Characteristics	Total	NOAC			Warfarin	p-value
		Regular dose	Reduced dose	All*		NOAC vs Warfarin
No. in group	**4,4236**	**5,491**	**6,120**	**11,611**	**32,625**	
Women	18,626 (42.1%)	2156 (39.3%)	3098 (50.6%)	5,254 (45.3%)	13,372 (41.0%)	<0.0001
Age	68.6 ±10.9	66.6 ±10.07	73.27 ±8.79	70.1 ±9.9	68.1 ±11.2	<0.0001
Age >65	30,908 (69.9%)	3556 (64.8%)	5265 (86.0%)	8,821 (76.0%)	22,087 (67.7%)	<0.0001
Age >75	14,164 (32.0%)	1134 (20.7%)	2911 (47.6%)	4,045 (34.8%)	10,119 (31.0%)	<0.0001
CHA_2DS_2-VASc score	3.47 ±1.3	3.27 ±1.23	3.83 ±1.32	3.57 ±1.31	3.43 ±1.3	<0.0001
2	12,663 (28.6%)	1820 (33.2%)	1105 (18.1%)	2,925 (25.2%)	9,738 (29.9%)	
3	12,198 (27.6%)	1648 (30.0%)	1580 (25.8%)	3,228 (27.8%)	8,970 (27.5%)	
4	9,720 (22.0%)	1128 (20.5%)	1559 (25.5%)	2,687 (23.1%)	7,033 (21.6%)	
≥ 5	9,655 (21.8%)	895 (16.3%)	1876 (30.7%)	2,771 (23.9%)	6,884 (21.1%)	
Hypertension	33,678 (76.1%)	4245 (77.3%)	4608 (75.3%)	8,853 (76.3%)	24,825 (76.1%)	0.737
Diabetes	11,051 (25.0%)	1408 (25.6%)	1452 (23.7%)	2,860 (24.6%)	8,191 (25.1%)	0.3102
Dyslipidemia	18,261 (41.3%)	2501 (45.6%)	2667 (43.6%)	5,168 (44.5%)	13,093 (40.1%)	<0.0001
Heart failure	21,328 (48.2%)	2395 (43.6%)	2748 (44.9%)	5,143 (44.3%)	16,185 (49.6%)	<0.0001
Myocardial infarction	2,072 (4.7%)	224 (4.10%)	295 (4.8%)	519 (4.5%)	1,553 (4.8%)	0.2037
Chronic obstructive pulmonary disease	9,027 (20.4%)	1002 (18.3%)	1450 (23.7%)	2,452 (21.1%)	6,575 (20.2%)	0.0268
Peripheral artery disease	6,030 (13.6%)	852 (15.5%)	1078 (17.6%)	1,930 (16.6%)	4,100 (12.6%)	<0.0001
Follow-up (years)	1.25 ±0.71	0.51 ±0.51	0.48 ±0.51	0.5 ±0.51	1.52 ±0.56	<0.0001

Supplementary Table III. Interaction p-values

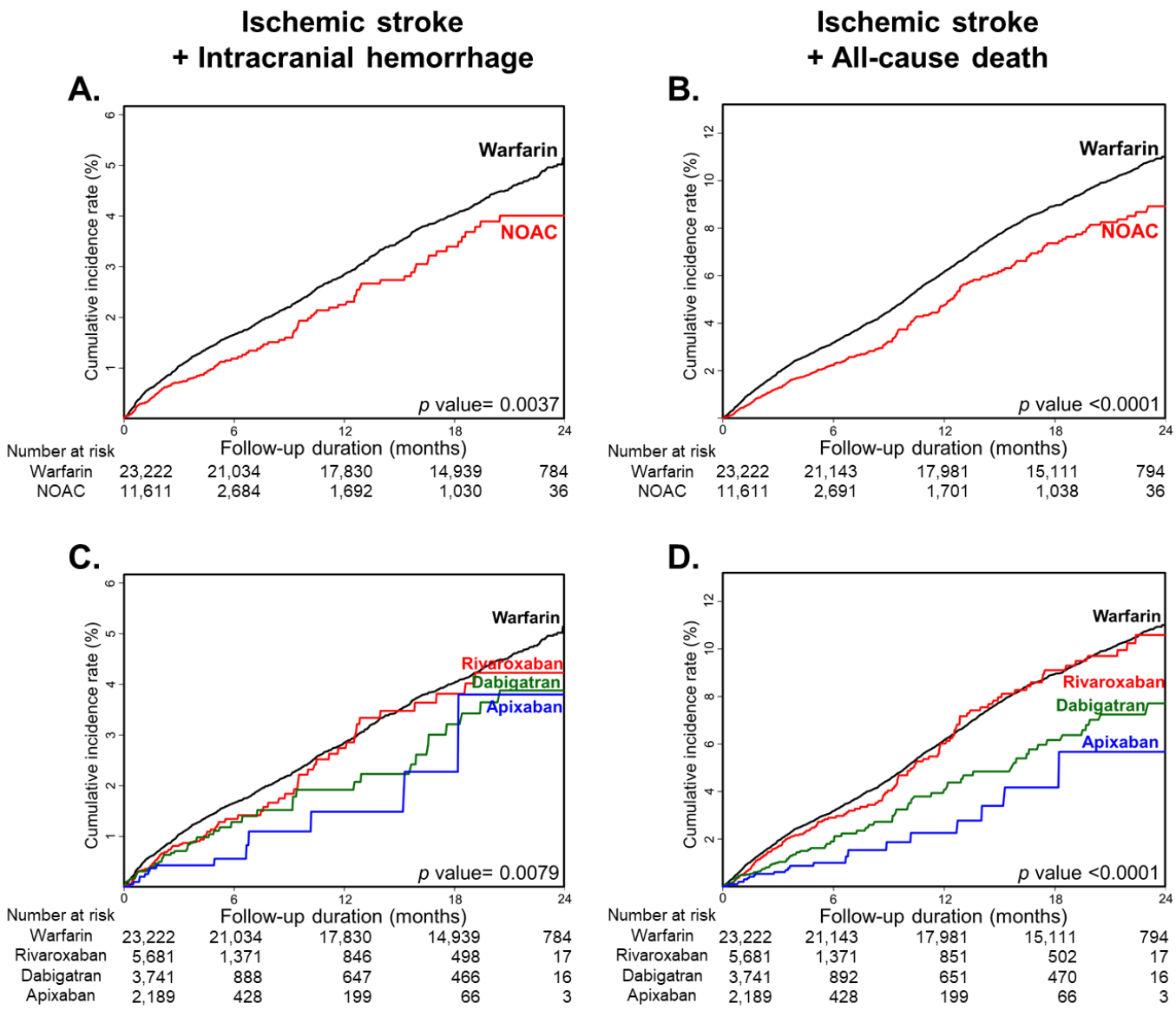
	Ischemic stroke	ICH*	All-cause death	Ischemic stroke + ICH	Ischemic stroke + all-cause death	Ischemic stroke + ICH + All-cause death
Sex (Male vs. Female)	0.288	0.382	0.277	0.499	0.686	0.548
Age (age < 65 vs. ≥ 65)	0.437	0.380	0.996	0.355	0.121	0.206
CHA_2DS_2-VASc score (score 2 vs. ≥ 3)	0.275	0.995	0.132	0.264	0.336	0.409

*ICH, intracranial hemorrhage

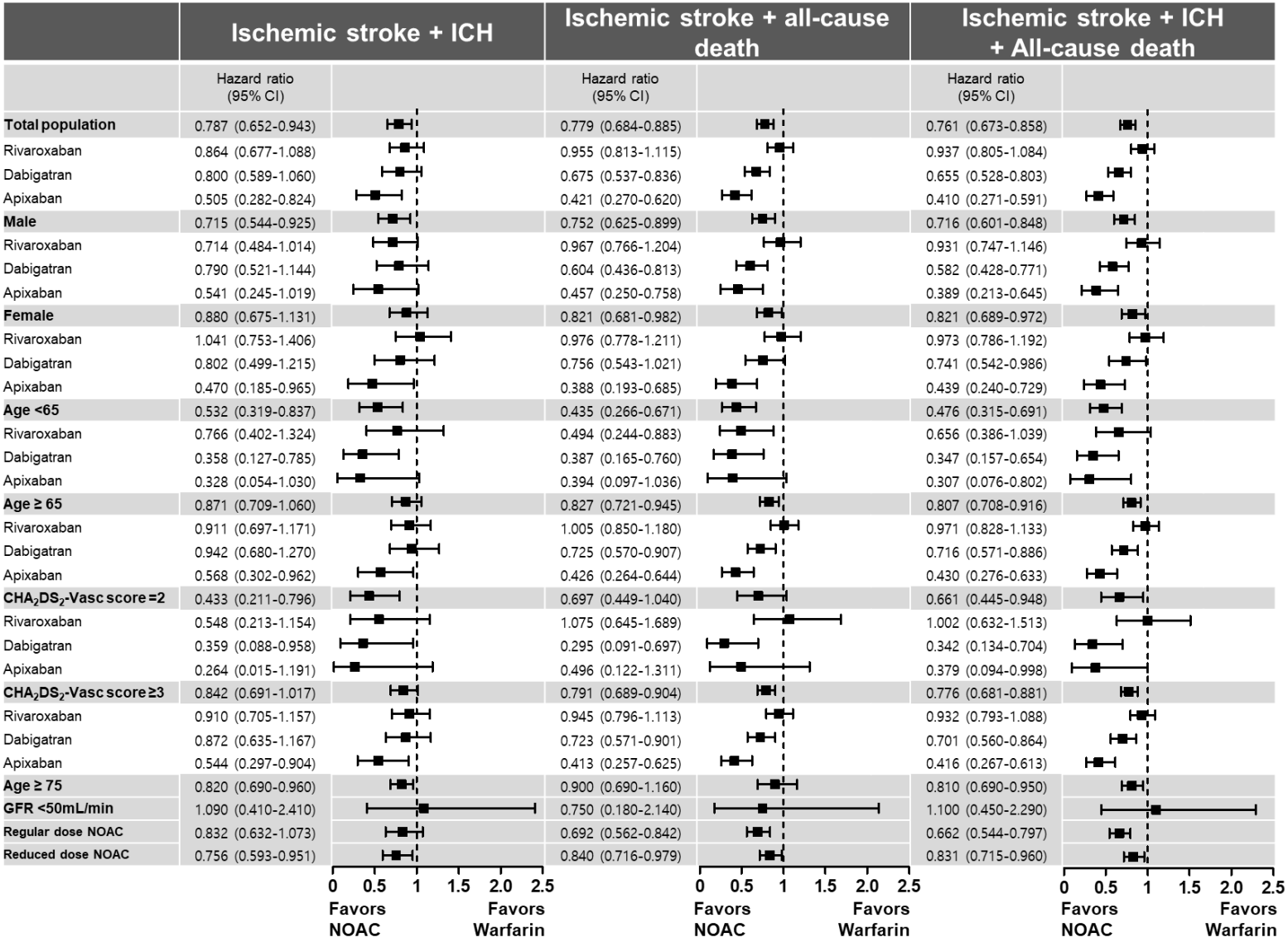
Supplementary Table IV. Oral anticoagulant-naïve Patient characteristics according to treatment

Characteristics	Total	NOAC				Warfarin	p-value
		Rivaroxaban	Dabigatran	Apixaban	All		NOAC vs Warfarin
No. in group	**23,262**	**5,116**	**3,168**	**2,066**	**10,350**	**12,912**	
Women	9,978 (42.9%)	2,434 (47.6%)	1,344 (42.4%)	955 (46.2%)	4,733 (45.7%)	5,245 (40.6%)	<0.0001
Age	68.9 ±11.1	70.6 ±9.8	69.4 ±9.9	70.5 ±9.9	70.2±9.9	67.9 ±11.9	<0.0001
Age >65	16,454 (70.7%)	1,832 (35.8%)	1,030 (32.5%)	762 (36.9%)	3,624 (35.0%)	4,110 (31.8%)	<0.0001
Age >75	7,734 (33.3%)	2,682 (52.4%)	1,824 (57.6%)	1,111 (53.8%)	5,617 (54.3%)	7,667 (59.4%)	<0.0001
CHA_2DS_2-VASc score	3.59 ±1.36	3.62 ±1.33	3.51 ±1.29	3.58 ±1.28	3.58 ±1.31	3.61 ±1.4	0.1787
2	6,051 (26.0%)	1,234 (24.1%)	841 (26.6%)	490 (23.7%)	2,565 (24.8%)	3,486 (27.0%)	
3	6,265 (26.9%)	1,394 (27.2%)	907 (28.6%)	585 (28.3%)	2,886 (27.9%)	3,379 (26.2%)	
4	5,095 (21.9%)	1,183 (23.1%)	707 (22.3%)	503 (24.4%)	2,393 (23.1%)	2,702 (20.9%)	
≥ 5	5,851 (25.2%)	1,305 (25.5%)	713 (22.5%)	488 (23.6%)	2,506 (24.2%)	3,345 (25.9%)	
Hypertension	17,778 (76.4%)	3,862 (75.5%)	2,408 (76.0%)	1,584 (76.7%)	7,854 (75.9%)	9,924 (76.9%)	0.0818
Diabetes	5,568 (23.9%)	1,201 (23.5%)	797 (25.2%)	489 (23.7%)	2,487 (24.0%)	3,081 (23.9%)	0.7661
Dyslipidemia	9,960 (42.8%)	2,216 (43.3%)	1,454 (45.9%)	929 (44.97)	4,599 (44.4%)	5,361 (41.5%)	<0.0001
Heart failure	11,200 (48.2%)	2,277 (44.5%)	1,391 (43.9%)	886 (42.88)	4,554 (44.0%)	6,646 (51.5%)	<0.0001
Myocardial infarction	1,321 (5.7%)	227 (4.4%)	144 (4.6%)	113 (5.47)	484 (4.7%)	837 (6.5%)	<0.0001
Chronic obstructive pulmonary disease	5,229 (22.5%)	1,093 (21.4%)	640 (20.2%)	446 (21.6%)	2,179 (21.1%)	3,050 (23.6%)	<0.0001
Peripheral artery disease	3,875 (16.7%)	874 (17.1%)	571 (18.0%)	317 (15.3%)	1,762 (17.0%)	2,113 (16.4%)	0.1797
Follow-up (years)	0.78 ±0.59	0.41 ±0.4	0.38 ±0.34	0.38 ±0.35	0.4 ±0.37	1.08 ±0.55	<0.0001

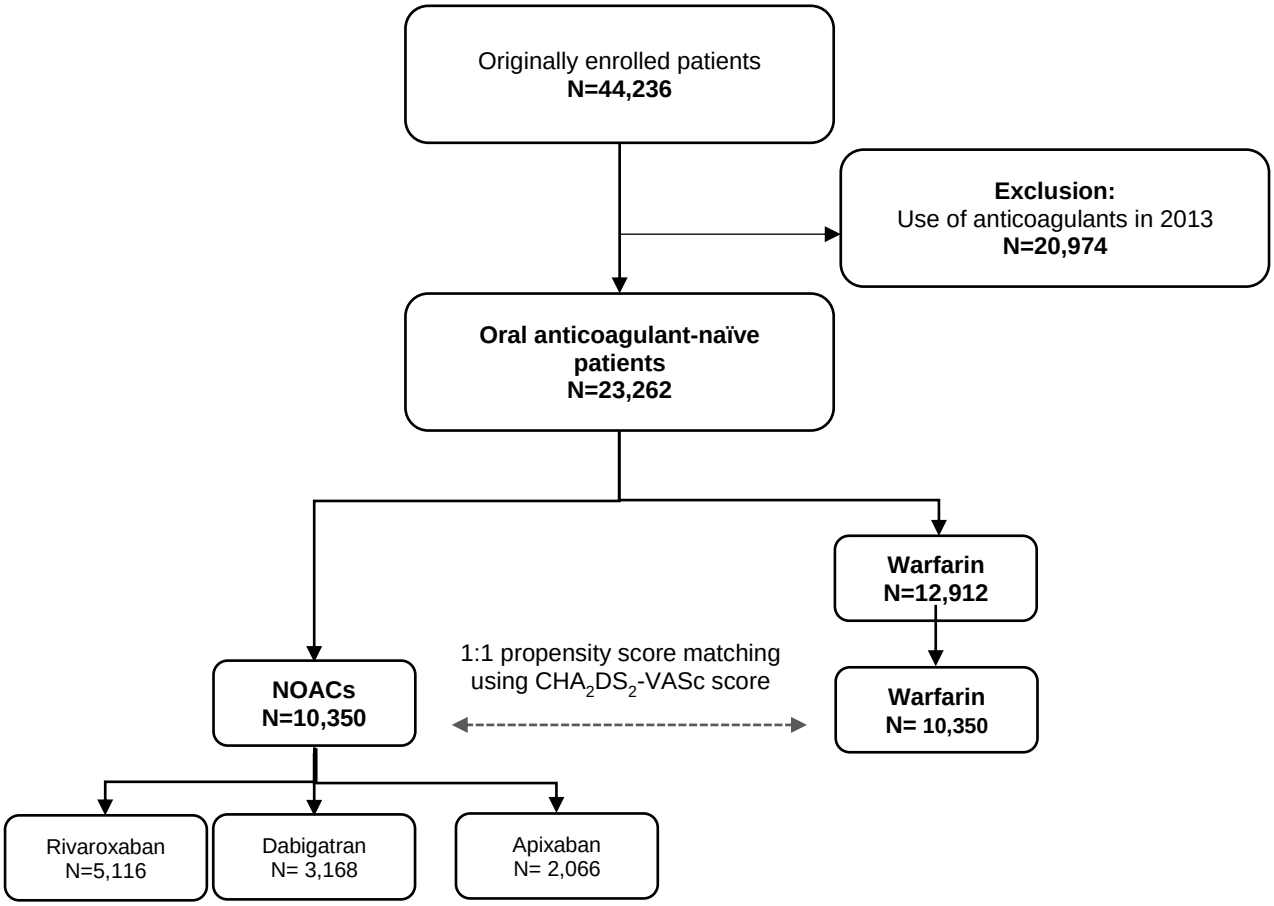
Supplementary figure I. Crude cumulative incidence curves of combined outcomes



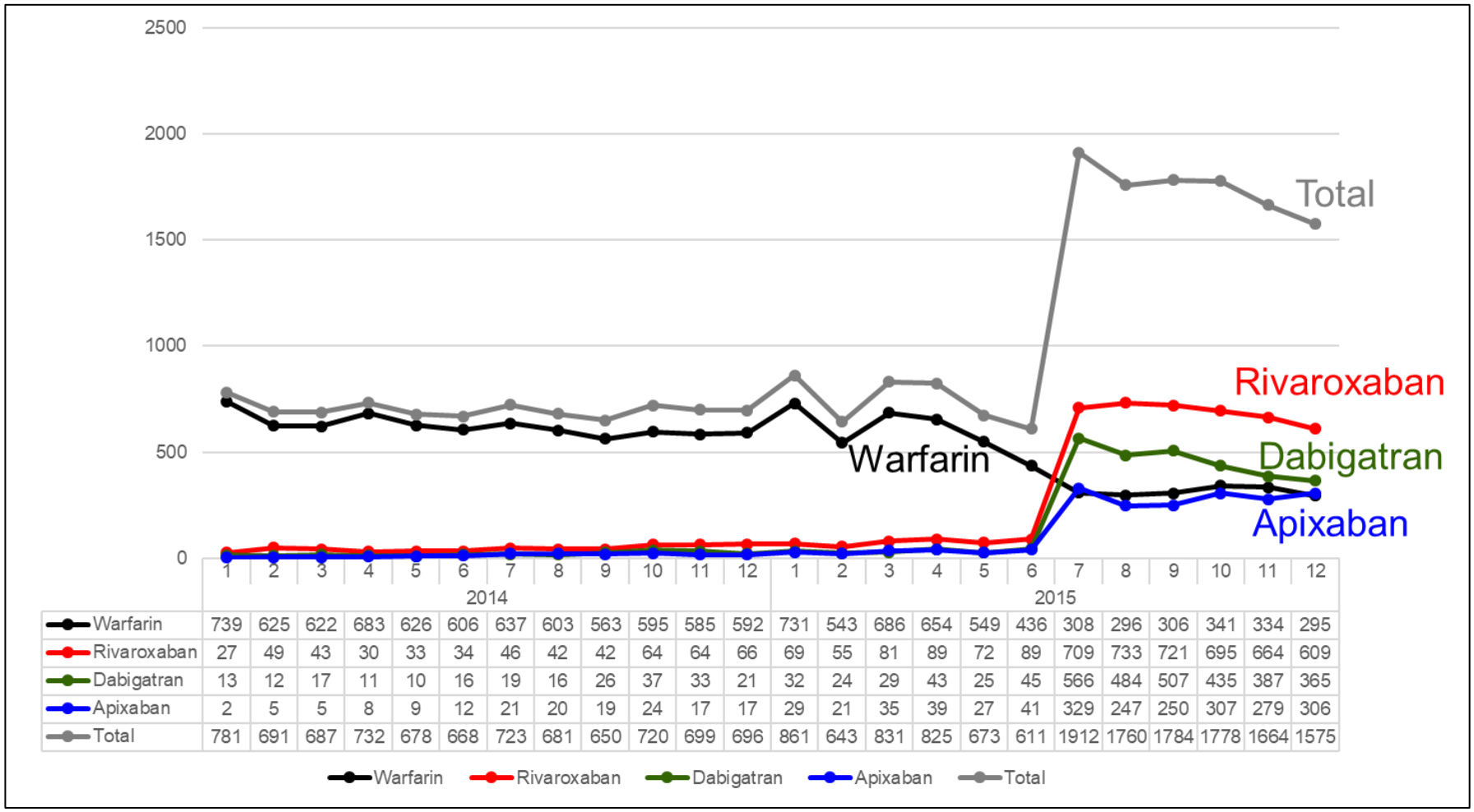
Supplementary figure II. Cox hazard ratios for overall follow-up for NOACs versus Warfarin for combined outcomes



Supplementary figure III. Oral anticoagulants-naive patient enrolment flow



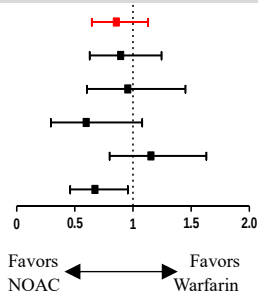
Supplementary figure IV. The distribution of new anticoagulant users during study period



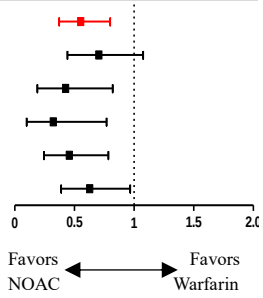
	2014												2015											
	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12
Warfarin	739	625	622	683	626	606	637	603	563	595	585	592	731	543	686	654	549	436	308	296	306	341	334	295
Rivaroxaban	27	49	43	30	33	34	46	42	42	64	64	66	69	55	81	89	72	89	709	733	721	695	664	609
Dabigatran	13	12	17	11	10	16	19	16	26	37	33	21	32	24	29	43	25	45	566	484	507	435	387	365
Apixaban	2	5	5	8	9	12	21	20	19	24	17	17	29	21	35	39	27	41	329	247	250	307	279	306
Total	781	691	687	732	678	668	723	681	650	720	699	696	861	643	831	825	673	611	1912	1760	1784	1778	1664	1575

Supplementary figure V. Number of events, crude/matched event rates, and Cox-regression hazard ratio according to treatment for oral anticoagulant-naïve patients

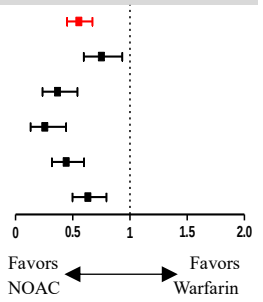
Treatment	No of patients	Events	IR*	Ischemic stroke HR (95% CI)
NOAC	10,350	77	1.9	0.857 (0.645,1.130)
Rivaroxaban	5,116	43	2.0	0.894 (0.628,1.246)
Dabigatran	3,168	24	2.0	0.956 (0.603,1.451)
Apixaban	2,066	10	1.3	0.598 (0.294,1.080)
Regular dose NOAC	5,481	40	2.0	1.155 (0.799,1.631)
Reduced dose NOAC	4,869	37	1.8	0.673 (0.461,0.956)
Warfarin (PS matched patients) †	1,0350	195	1.8	1.00
Warfarin (Overall patients)	12,912	278	2.0	-



Treatment	No of patients	Events	IR*	Intracranial hemorrhage HR (95% CI)
NOAC	10,350	36	0.9	0.553 (0.373,0.800)
Rivaroxaban	5,116	24	1.1	0.705 (0.442,1.077)
Dabigatran	3,168	8	0.7	0.426 (0.190,0.821)
Apixaban	2,066	4	0.5	0.323 (0.099,0.770)
Regular dose NOAC	5,481	13	0.6	0.457 (0.244,0.785)
Reduced dose NOAC	4,869	23	1.1	0.628 (0.390,0.968)
Warfarin (PS matched patients) †	1,0350	151	1.4	1.00
Warfarin (Overall patients)	12,912	198	1.4	-



Treatment	No of patients	Events	IR*	All-cause death HR (95% CI)
NOAC	10,350	128	3.1	0.554 (0.452,0.673)
Rivaroxaban	5,116	93	4.3	0.750 (0.596,0.934)
Dabigatran	3,168	24	2.0	0.367 (0.236,0.542)
Apixaban	2,066	11	1.4	0.256 (0.132,0.443)
Regular dose NOAC	5,481	43	2.1	0.443 (0.318,0.599)
Reduced dose NOAC	4,869	85	4.0	0.633 (0.498,0.795)
Warfarin (PS matched patients) †	1,0350	628	5.6	1.00
Warfarin (Overall patients)	12,912	800	5.7	-



*IR, incidence rate, events divided by 100 person years (%/year); †Reference for hazard ratio

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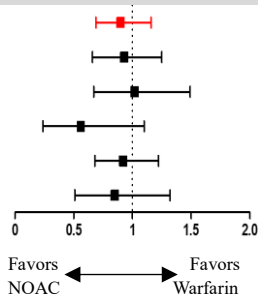
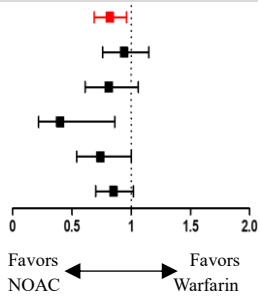
Supplementary figure V: Continued

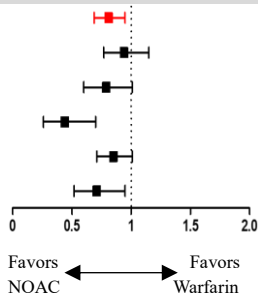
Treatment	No of patients	Events	IR*	Ischemic stroke + Intracranial hemorrhage HR (95% CI)
NOAC	10,350	107	2.6	0.737 (0.582,0.925)
Rivaroxaban	5,116	63	3.0	0.820 (0.615,1.076)
Dabigatran	3,168	31	2.6	0.751 (0.505,1.078)
Apixaban	2,066	13	1.7	0.475 (0.258,0.798)
Regular dose NOAC	5,481	50	2.5	0.844 (0.613,1.139)
Reduced dose NOAC	4,869	57	2.7	0.663 (0.491,0.880)
Warfarin (PS matched patients) †	1,0350	319	2.9	1.00
Warfarin (Overall patients)	12,912	437	3.2	-



Treatment	No of patients	Events	IR*	Ischemic stroke + All-cause death HR (95% CI)
NOAC	10,350	198	4.8	0.635 (0.537,0.747)
Rivaroxaban	5,116	131	6.2	0.785 (0.646,0.947)
Dabigatran	3,168	47	3.9	0.535 (0.391,0.713)
Apixaban	2,066	20	2.6	0.344 (0.213,0.523)
Regular dose NOAC	5,481	80	4.0	0.628 (0.492,0.790)
Reduced dose NOAC	4,869	118	5.6	0.640 (0.521,0.778)
Warfarin (PS matched patients) †	1,0350	782	7.1	1.00
Warfarin (Overall patients)	12,912	1,019	7.4	-



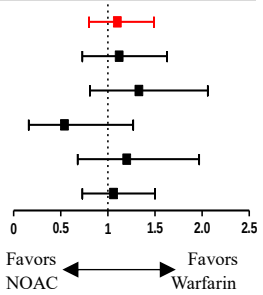
Treatment	No of patients	Events	IR*	Ischemic stroke + Intracranial hemorrhage + All-cause death HR (95% CI)
NOAC	10,350	227	5.6	0.634 (0.542,0.737)
Rivaroxaban	5,116	151	7.1	0.792 (0.660,0.944)
Dabigatran	3,168	53	4.4	0.521 (0.388,0.683)
Apixaban	2,066	23	2.9	0.343 (0.219,0.507)
Regular dose NOAC	5,481	90	4.5	0.606 (0.482,0.753)
Reduced dose NOAC	4,869	137	6.5	0.653 (0.540,0.783)
Warfarin (PS matched patients) †	1,0350	871	8.0	1.00
Warfarin (Overall patients)	12,912	1,136	8.3	-



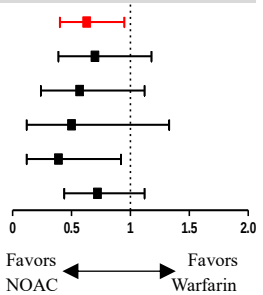
*IR, incidence rate, events divided by 100 person years (%/year); †Reference for hazard ratio

Supplementary figure VI. Number of events, crude/matched event rates, and Cox-regression hazard ratio of elderly patients with age ≥75 years old

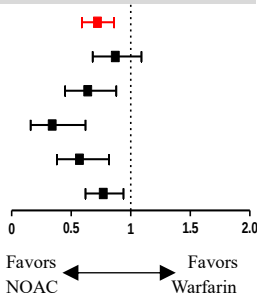
Treatment	No of patients	Events	IR*	Ischemic stroke HR (95% CI)
NOAC	4,045	52	2.7	1.10 (0.80,1.49)
Rivaroxaban	2,029	28	2.9	1.12 (0.73,1.63)
Dabigatran	1,215	20	3.2	1.33 (0.81,2.06)
Apixaban	801	4	1.4	0.54 (0.16,1.27)
Regular dose NOAC	1,134	37	2.9	1.20 (0.68,1.97)
Reduced dose NOAC	2,911	15	2.7	1.06 (0.73,1.50)
Warfarin (PS matched patients) †	7,828	261	2.3	1.00
Warfarin (Overall patients)	10,119	331	2.3	-



Treatment	No of patients	Events	IR*	Intracranial hemorrhage HR (95% CI)
NOAC	4,045	24	1.3	0.63 (0.40,0.95)
Rivaroxaban	2,029	14	0.6	0.70 (0.39,1.18)
Dabigatran	1,215	7	0.4	0.57 (0.24,1.12)
Apixaban	801	3	0.2	0.50 (0.12,1.33)
Regular dose NOAC	1,134	4	0.8	0.39 (0.12,0.92)
Reduced dose NOAC	2,911	20	1.4	0.72 (0.44,1.12)
Warfarin (PS matched patients) †	7,828	210	1.9	1.00
Warfarin (Overall patients)	10,119	268	1.8	-



Treatment	No of patients	Events	IR*	All-cause death HR (95% CI)
NOAC	4,045	126	6.7	0.72 (0.59,0.86)
Rivaroxaban	2,029	80	8.1	0.87 (0.68,1.09)
Dabigatran	1,215	37	6.0	0.64 (0.45,0.88)
Apixaban	801	9	3.1	0.34 (0.16,0.62)
Regular dose NOAC	1,134	27	5.3	0.57 (0.38,0.82)
Reduced dose NOAC	2,911	99	7.2	0.77 (0.62,0.94)
Warfarin (PS matched patients) †	7,828	1093	9.5	1.00
Warfarin (Overall patients)	10,119	1413	9.6	-



*IR, incidence rate, events divided by 100 person years (%/year); †Reference for hazard ratio

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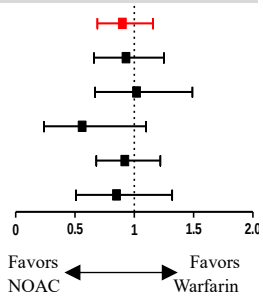
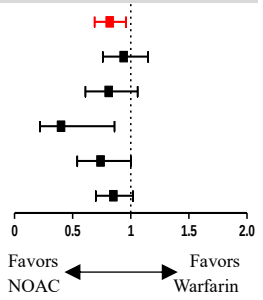
Supplementary figure VI: Continued

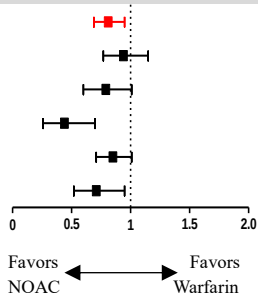
Treatment	No of patients	Events	IR*	HR (95% CI)
			Ischemic stroke + Intracranial hemorrhage	
NOAC	4,045	72	3.8	0.90 (0.69,1.16)
Rivaroxaban	2,029	39	4.0	0.93 (0.66,1.25)
Dabigatran	1,215	26	4.2	1.02 (0.67,1.49)
Apixaban	801	7	2.4	0.56 (0.24,1.10)
Regular dose NOAC	1,134	18	3.5	0.92 (0.68,1.22)
Reduced dose NOAC	2,911	54	3.9	0.85 (0.51,1.32)
Warfarin (PS matched patients) †	7,828	437	3.9	1.00
Warfarin (Overall patients)	10,119	550	3.8	-



Treatment	No of patients	Events	IR*	HR (95% CI)
			Ischemic stroke + All-cause death	
NOAC	4,045	174	9.2	0.82 (0.69,0.96)
Rivaroxaban	2,029	105	10.7	0.94 (0.76,1.15)
Dabigatran	1,215	56	9.1	0.81 (0.61,1.06)
Apixaban	801	13	4.6	0.40 (0.22,0.86)
Regular dose NOAC	1,134	42	8.2	0.74 (0.54,1.00)
Reduced dose NOAC	2,911	132	9.6	0.85 (0.70,1.02)
Warfarin (PS matched patients) †	7,828	1252	11.1	1.00
Warfarin (Overall patients)	10,119	1615	11.1	-

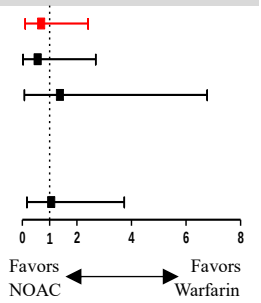


Treatment	No of patients	Events	IR*	HR (95% CI)
			Ischemic stroke + Intracranial hemorrhage + All-cause death	
NOAC	4,045	192	10.3	0.81 (0.69,0.95)
Rivaroxaban	2,029	116	11.9	0.94 (0.77,1.15)
Dabigatran	1,215	60	9.6	0.79 (0.60,1.01)
Apixaban	801	16	5.6	0.44 (0.26,0.70)
Regular dose NOAC	1,134	45	3.9	0.85 (0.71,1.01)
Reduced dose NOAC	2,911	147	10.3	0.71 (0.52,0.95)
Warfarin (PS matched patients) †	7,828	1358	12.1	1.00
Warfarin (Overall patients)	10,119	1746	12.0	-

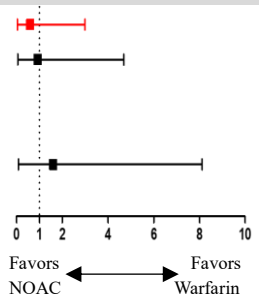


Supplementary figure VII. Number of events, crude/matched event rates, and Cox-regression hazard ratio of patients with decreased renal function (GFR <50mL/min)

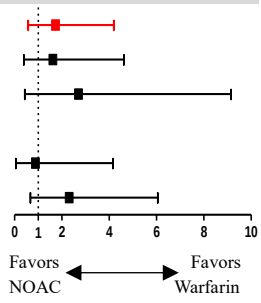
Treatment	No of patients	Events	IR*	Ischemic stroke HR (95% CI)
NOAC	355	2	1.1	0.69 (0.11,2.41)
Rivaroxaban	199	1	0.9	0.56 (0.03,2.69)
Dabigatran	88	1	2.3	1.38 (0.08,6.78)
Apixaban	68	0	-	-
Regular dose NOAC	118	0	-	-
Reduced dose NOAC	237	2	1.8	1.06 (0.17,3.74)
Warfarin (PS matched patients) †	723	25	1.6	1.00
Warfarin (Overall patients)	964	35	1.7	-



Treatment	No of patients	Events	IR*	Intracranial hemorrhage HR (95% CI)
NOAC	355	1	0.6	0.59 (0.03,2.99)
Rivaroxaban	199	1	0.9	0.92 (0.05,4.69)
Dabigatran	88	0	-	-
Apixaban	68	0	-	-
Regular dose NOAC	118	1	1.5	1.60 (0.09,8.11)
Reduced dose NOAC	237	0	-	-
Warfarin (PS matched patients) †	723	16	1.0	1.00
Warfarin (Overall patients)	964	20	1.0	-



Treatment	No of patients	Events	IR*	All-cause death HR (95% CI)
NOAC	355	5	2.8	1.73 (0.58,4.19)
Rivaroxaban	199	3	2.7	1.62 (0.39,4.62)
Dabigatran	88	2	4.5	2.70 (0.43,9.16)
Apixaban	68	0	-	-
Regular dose NOAC	118	1	1.5	0.88 (0.05,4.15)
Reduced dose NOAC	237	4	3.5	2.31 (0.67,6.05)
Warfarin (PS matched patients) †	723	33	2.1	1.00
Warfarin (Overall patients)	964	42	2.0	-



*IR, incidence rate, events divided by 100 person years (%/year); †Reference for hazard ratio

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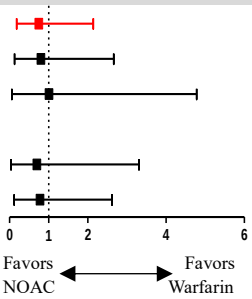
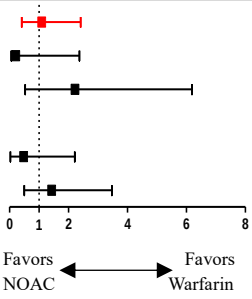
Supplementary figure VII: Continued

Treatment	No of patients	Events	IR*	Ischemic stroke + Intracranial hemorrhage HR (95% CI)
NOAC	355	3	1.7	0.75 (0.18,2.14)
Rivaroxaban	199	2	1.8	0.80 (0.13,2.66)
Dabigatran	88	1	2.3	1.01 (0.06,4.78)
Apixaban	68	0	-	-
Regular dose NOAC	118	1	1.5	0.70 (0.04,3.31)
Reduced dose NOAC	237	2	1.7	0.78 (0.12,2.62)
Warfarin (PS matched patients) †	723	37	2.4	1.00
Warfarin (Overall patients)	964	51	2.5	-



Treatment	No of patients	Events	IR*	Ischemic stroke + All-cause death HR (95% CI)
NOAC	355	6	3.4	1.09 (0.41,2.41)
Rivaroxaban	199	3	2.6	0.06 (0.21,2.37)
Dabigatran	88	3	6.1	2.22 (0.53,6.19)
Apixaban	68	0	-	-
Regular dose NOAC	118	1	1.5	0.48 (0.03,2.21)
Reduced dose NOAC	237	5	4.4	1.43 (0.50,3.47)
Warfarin (PS matched patients) †	723	55	3.6	1.00
Warfarin (Overall patients)	964	73	3.6	-



Treatment	No of patients	Events	IR*	Ischemic stroke + Intracranial hemorrhage + All-cause death HR (95% CI)
NOAC	355	7	4.0	1.10 (0.45,2.29)
Rivaroxaban	199	4	3.6	1.00 (0.50,2.45)
Dabigatran	88	3	4.9	1.69 (0.46,5.19)
Apixaban	68	0	-	-
Regular dose NOAC	118	2	3.1	0.36 (0.14,2.77)
Reduced dose NOAC	237	5	4.5	1.25 (0.43,2.53)
Warfarin (PS matched patients) †	723	65	4.3	1.00
Warfarin (Overall patients)	964	87	4.3	-