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ORIGINAL ARTICLE

Effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in atrial fibrillation: a Scandinavian population-based cohort study

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Aims Using Scandinavian population-based registries, we assessed risk of stroke/systemic embolism (SE) and bleeding with non-vitamin K antagonist oral anticoagulants compared with warfarin in anticoagulation-naïve patients with atrial fibrillation (AF).

Methods and results This historical cohort study included 219 545 AF patients [median age 74 years; 43% women; mean CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke or transient ischaemic attack, vascular disease, age 65–74 years, sex category) score 3.3] initiating apixaban, dabigatran, rivaroxaban, or warfarin in Denmark, Norway, and Sweden (1 January 2013 to 31 December 2016). The primary endpoints were stroke/SE and major bleeding. The median follow-up times were 9.7 (3.9–21.5) months for stroke/SE and 9.6 (3.8–21.3) months for bleeding. Apixaban and warfarin initiators were older and had higher CHA_2DS_2-VASc scores compared with dabigatran and rivaroxaban initiators. After 1:1 propensity score matching, three cohorts were created: apixaban–warfarin (n = 111 162), dabigatran–warfarin (n = 56 856), and rivaroxaban–warfarin (n = 61 198). Adjusted hazard ratios (HRs) were estimated using a Cox regression. For stroke/SE, adjusted HRs against warfarin were 0.96 [95% confidence interval (CI): 0.87–1.06] for apixaban, 0.89 (95% CI: 0.80–1.00) for dabigatran, and 1.03 (95% CI: 0.92–1.14) for rivaroxaban. For major bleeding, the HRs against warfarin were 0.73 (95% CI: 0.67–0.78) for apixaban, 0.89 (95% CI: 0.82–0.97) for dabigatran, and 1.15 (95% CI: 1.07–1.25) for rivaroxaban. The results in the dabigatran cohort did not hold in all dose-defined subgroups.

Conclusion In this large Scandinavian study among AF patients initiating oral anticoagulation, those initiating dabigatran, apixaban, and rivaroxaban had similar rates of stroke/SE to patients initiating warfarin. Rates of major bleeding were lower with apixaban and dabigatran and higher with rivaroxaban, each compared with warfarin.

Keywords Anticoagulants • Atrial fibrillation • Bleeding • Cohort study • Stroke

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Introduction

Current US and European guidelines recommend non-vitamin K antagonist oral anticoagulants (NOACs) over warfarin and other vitamin K antagonists (VKAs) as first-line treatment for stroke prevention in eligible patients with atrial fibrillation (AF).[1–3] These recommendations are based on the results of randomized clinical trials (RCTs), showing superior or comparable efficacy and safety of NOACs compared with warfarin.[4–8] Recently, several real-world studies have shown similar results to the RCTs with comparable or superior effectiveness and safety for NOACs compared with VKAs. However, the results have not been entirely consistent with respect to effectiveness or safety.[9–12] In the largest observational cohort study on NOACs and warfarin to date, the ARISTOPHANES (Anticoagulants for Reduction in Stroke: Observational Pooled Analysis on Health Outcomes and Experience of Patients) study,[11] treatment with rivaroxaban was associated with a significantly higher risk of major bleeding compared with warfarin, and treatments with apixaban, dabigatran, and rivaroxaban were associated with significantly lower rates of stroke/systemic embolism (SE). Furthermore, previous real-world studies were performed on data from health insurance databases or other more selective registries.[9] More studies are needed from unselected patient populations to improve generalizability.[13] Denmark, Norway, and Sweden have tax-funded universal healthcare and routinely recorded data on hospital admissions, hospital clinic outpatient visits, dispensed prescriptions, and vital status through national registries and databases.[14–16] Linkage of individual-level data across diverse data sources is enabled via unique personal identifiers in each Scandinavian country. This set-up has the benefit of allowing complete follow-up of individuals with virtually no selection bias. Moreover, Scandinavian countries have high-quality warfarin treatment, thus representing an especially suitable setting for assessing the effectiveness and safety of NOACs against well-managed warfarin.[17,18] Several previous real-world Scandinavian studies comparing NOACs with warfarin were restricted to data from individual countries.[10,12,19,20] The aim of this study was to examine the effectiveness and safety of NOACs compared with warfarin among oral anticoagulation (OAC)-naïve patients with AF in a large unselected Scandinavian cohort. The current study extends previous evidence by pooling patient-level data across the three Scandinavian countries, providing the benefits of increasing the study size, facilitating robust analyses of endpoints, and supporting subgroup analyses.

Methods

Study design and setting

This historical cohort study was based on routinely and prospectively collected data from population-based health registries in Denmark, Norway, and Sweden. The study was registered at the European Union electronic Register of Post-Authorisation Studies (EUPAS13470).

Data sources

Data originated from the Danish National Patient Registry, Danish National Health Service Prescription Database, Danish Civil Registration System, Norwegian Patient Registry, Norwegian Prescription Database, National Population Register of Norway, Swedish National Patient Register, Swedish Prescribed Drug Register, Swedish Total Population Register, and Swedish Cause of Death Register.

National patient registries contain information on primary and secondary hospital discharge diagnoses, coded according to the International Classification of Diseases, 10th Revision (ICD-10),[21] and data on surgical procedures, coded according to the Nordic Medico-Statistical Committee coding system.[22] Dispensing in prescription registries is coded using the Anatomical Therapeutic Chemical classification.[23] The population registries hold information on residence and vital status. Diagnosis, procedure, and drug codes used are shown in Supplementary material online, *Table S1*. Data from the Scandinavian national registries have been validated, and validity has generally been found to be high in all countries.[23–26]

Study population

We included OAC-naïve patients aged ≥18 years initiating apixaban, rivaroxaban, dabigatran, or warfarin from 1 January 2013 through 31 December 2016. For each patient, the index date was the date of dispensing of the first OAC. Patients were required to have a diagnosis of AF recorded ≤5 years before or ≤60 days after the index date. Registry-based diagnosis codes in the Scandinavian countries have high validity, with positive predictive values in the 89–97% range.[27–29] Patients with mitral stenosis or presence of mechanical heart valves in the previous 5 years and patients dispensed any OAC within 12 months before the index date were excluded. Additional exclusion criteria are presented in *Figure 1*.

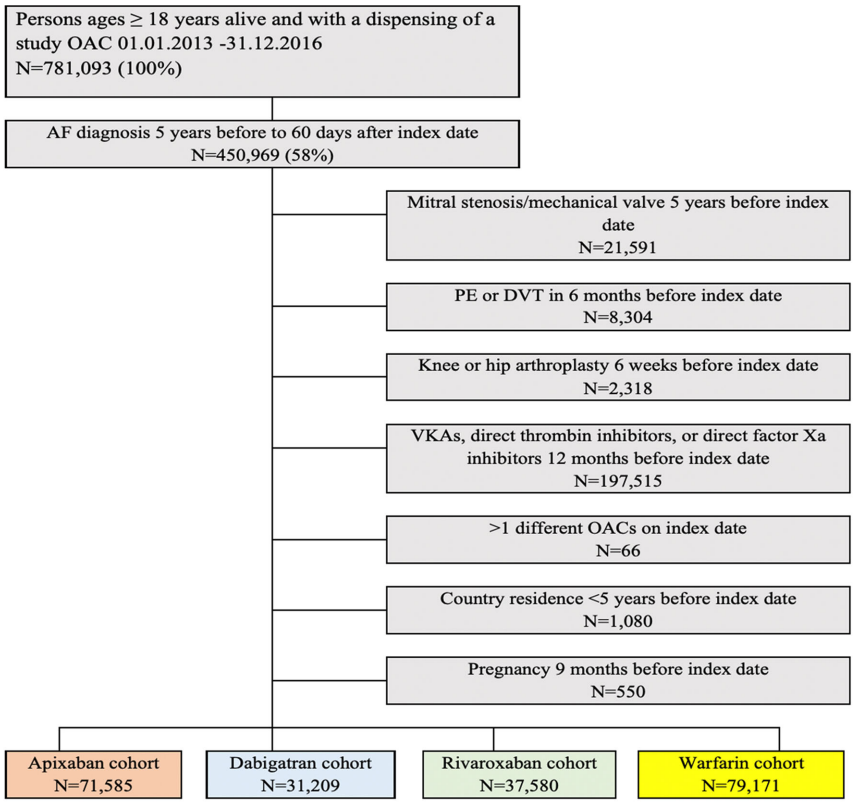
Oral anticoagulant supply

For each OAC, the days of supply were computed using information on dates of dispensing, the pack size dispensed, and the number of packages. For each patient, the on-treatment period was defined as the index date plus days of supply with an additional 30-day grace period to account for incomplete adherence and allowing for stockpiling from one period to another. The days of supply per patient were calculated as the total amount dispensed divided by the daily dose. The NOACs are prescribed in fixed doses to be taken once daily (rivaroxaban) or twice daily (dabigatran, apixaban); i.e. the daily dose equals one pill or two pills, respectively.[19] To approximate the daily dose for warfarin in the absence of data on dosing instructions and international normalized ratio (INR) reference values, the following approach was used. The total amount of warfarin dispensed was calculated as warfarin tablet strength dispensed multiplied by the number of warfarin tablets in a package and multiplied by the number of packages dispensed. The expected daily dose was calculated as the median within age group of person-specific mean daily doses (age at index date <55 years, 55 to <65 years, 65 to <75 years, 75 to <85 years, ≥85 years) for each country.[19]

Switching was defined as a patient who was dispensed an OAC different from the index OAC. Discontinuation was defined as no dispensing of the index OAC >30 days after the estimated end of supply.

Comorbidity and concomitant pharmacotherapy

Baseline characteristics of the study population were ascertained during up to 5 years before and including the index date. The ICD-10 codes included for each diagnosis are given in Supplementary material online, *Table S1*. Baseline concomitant medication use was assessed using dispensing records within 90 days of the index date.



AF: atrial fibrillation, DVT: deep vein thrombosis, OAC: oral anticoagulant, PE: pulmonary embolism, VKA: vitamin K antagonist.

Figure 1 Flow diagram for creation of the study population. AF, atrial fibrillation; DVT, deep vein thrombosis; OAC, oral anticoagulant; PE, pulmonary embolism; and VKA, vitamin K antagonist.

Outcomes

The primary effectiveness endpoint was a composite of any stroke (ischaemic or haemorrhagic) or SE requiring an acute hospitalization with an overnight stay. The primary safety endpoint was major bleeding, defined as any bleeding (intracranial, gastrointestinal, or other) requiring acute hospitalization with an overnight stay. Secondary endpoints included the following events requiring an acute hospitalization with an overnight stay: ischaemic stroke, haemorrhagic stroke, intracranial bleeding, and gastrointestinal bleeding. The ICD-10 codes used for the identification of the outcomes are listed in Supplementary material online, *Table S2*. Patients were followed until death, emigration, treatment switch or discontinuation, or 31 December 2016, whichever occurred first.

Statistical methods

Main analyses

Continuous variables were described by mean and standard deviation (SD) or median and interquartile range (IQR). Categorical variables were summarized as frequencies and proportions. CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke or transient ischaemic attack, vascular disease, age 65–74 years, sex category) and modified HAS-BLED (hypertension, abnormal renal or liver function, stroke, bleeding, labile INR, elderly, drug or alcohol usage) scores were computed using the definitions in Supplementary material online, *Table S1*. For all primary and secondary endpoints, crude cumulative incidences over the available follow-up and 95% confidence intervals (CIs) within each OAC cohort were computed while treating death as a competing risk; follow-up was censored at death, emigration, treatment switch or discontinuation, or 31 December 2016, whichever occurred first.

To compare the risks for the primary and secondary endpoints among initiators of each NOAC vs. warfarin, a Cox proportional hazards regression was used. For each patient, a propensity score (PS) was estimated via logistic regression, as the probability of receiving the given NOAC vs. warfarin, given the covariates (see Supplementary material online, *Table S1*), entered into the model as first-order terms. For each initiator of a given NOAC, initiators of warfarin were matched 1:1, without replacement, using a calliper of width equal to 0.2 of the SD of the logit of the PS.[30] Three NOAC–warfarin PS-matched cohorts were constructed: apixaban–warfarin, dabigatran–warfarin, and rivaroxaban–warfarin. Within each matched population, the balance of the measured covariates was assessed by examining standardized mean differences (SMDs) before and after the matching. A SMD < 0.1 was considered indicative of balance for a given covariate. Members of the NOAC cohorts without a match were excluded from the PS-matched analyses.

The analyses were conducted on a pooled individual-level dataset. Separate input datasets for each of the three countries were prepared according to a common data model. The input datasets from all countries were transferred and combined for analysis on a secure server at Statistics Denmark and analysed using SAS Software version 9.4 (SAS Inc., Cary, NC, USA).

Subgroup analyses

The consistency of the results for primary endpoints was evaluated according to the following subgroups: by age on index date (<65 years, 65 to <75 years, 75 to <85 years, ≥85 years); by sex; according to CHA_2DS_2-VASc and modified HAS-BLED score categories at baseline; in patients with/without chronic kidney disease, diabetes, heart failure, coronary artery disease, and prior stroke at baseline; in each country; and according to the initial dosage (standard vs. reduced dose; standard dose is apixaban: 5 mg twice daily; dabigatran: 150 mg twice daily; rivaroxaban: 20 mg once daily; reduced dose is apixaban: 2.5 mg twice daily; dabigatran: ≤110 mg twice daily; rivaroxaban: 15 mg once daily). A Cox proportional hazards regression model was fit including, in addition to the treatment variable, a subgroup-by-treatment interaction term. Within each subgroup, covariates with a SMD ≥ 0.1 were included in the regression model to estimate the subgroup-specific adjusted hazard ratios (HRs) and 95% CIs. Subgroup-specific adjusted HRs with <10 events per degree of freedom were not estimated to avoid unstable estimates. For the analyses stratified on the initial dose, *de novo* PS matching within the initial dose-defined subgroups was performed.

Sensitivity analyses

Three sensitivity analyses were performed: (i) intention-to-treat (ITT)-like analyses—the overall PS-matched analyses to estimate HRs of the primary endpoints were repeated without censoring by treatment switch or discontinuation; (ii) the comparative analyses of the primary endpoints in the PS-matched population were repeated using an alternative definition of warfarin discontinuation based on maximum likelihood estimation of a parametric two-component mixture model for the waiting time distribution (as recently described in a similar setting and using data on the percentiles of the waiting time distribution previously reported for Danish patients);[31,32] and (iii) the comparative analyses of the primary endpoints were repeated in the full dataset using a conventional multivariable Cox proportional hazards regression instead of PS matching to avoid exclusion of non-matched patients.

Ethics

The study complied with legal and regulatory requirements and was approved by the Danish Data Protection Agency (Aarhus University registration number 2016-051-000001/450), the Norwegian Regional Committee for Medical and Health Research Ethics, Region West (ref no. 2015/1503), the Norwegian Data Protection Agency (ref no. 17/01153), and the Regional Ethical Board in Stockholm, Sweden (record numbers 2013/1850-31/1, 2014/1214-32, and 2016/2218-32).

Results

Description of the study population

We included 219 545 patients (*Figure 1*): 71 585 patients initiated apixaban, 31 209 patients dabigatran, 37 580 patients rivaroxaban, and 79 171 patients initiated warfarin. Supplementary material online, *Table S3* shows the baseline characteristics of the unmatched cohorts. Apixaban and warfarin initiators were older and had higher CHA_2DS_2-VASc scores compared with dabigatran and rivaroxaban initiators; apixaban and warfarin patients were also more likely to have a Charlson comorbidity index score of ≥3. Between one-quarter and one-third of the NOAC initiators were started on a reduced dose. The overall median (IQR) follow-up time until censoring, an endpoint, or death ranged from 9.6 (3.8, 21.3) to 9.9 (3.9, 21.7) months. Median follow-up times until stroke/SE and major bleeding for each OAC are presented in Supplementary material online, *Table S3*. Crude incidence rates per 100 person-years (95% CI) for stroke/SE (for each OAC) were as follows: apixaban, 2.1 (2.0–2.2); dabigatran, 1.4 (1.3–1.5); rivaroxaban, 1.9 (1.8–2.1); and warfarin, 1.9 (1.8–2.0). Crude incidence rates per 100 person-years (95% CI) for major bleeding (for each OAC) were as follows: apixaban, 3.0 (2.9–3.2); dabigatran, 2.5 (2.3–2.6); rivaroxaban, 3.9 (3.7–4.1); and warfarin, 3.5 (3.4–3.6).

PS-matched cohorts

After the PS matching, 111 162 patients were included in the apixaban–warfarin cohort, 56 856 in the dabigatran–warfarin cohort, and 61 198 in the rivaroxaban–warfarin cohort. Overall, proportions of the NOAC initiators with a match were 78% for apixaban, 91% for dabigatran, and 81% for rivaroxaban. Baseline characteristics of the three PS-matched cohorts were balanced (*Table 1*). The median age was highest in the apixaban–warfarin cohort and lowest in the dabigatran–warfarin cohort. The cumulative incidence of stroke/SE and major bleeding in each cohort is shown in *Figure 2*.

For apixaban vs. warfarin, adjusted HR for stroke/SE was 0.96 (95% CI: 0.87–1.06) and adjusted HR for major bleeding was 0.73 (95% CI: 0.67–0.78). For dabigatran vs. warfarin, adjusted HR for stroke/SE was 0.89 (95% CI: 0.80–1.00) and the adjusted HR for major bleeding was 0.89 (95% CI: 0.82–0.97). For rivaroxaban vs. warfarin, adjusted HR for stroke/SE was 1.03 (95% CI: 0.92–1.14) and adjusted HR for major bleeding was 1.15 (95% CI: 1.07–1.25). *Figure 3* shows results for the overall stroke and bleeding outcomes and their subtypes.

Subgroup analyses

Pairwise PS-matched adjusted HRs of the primary endpoints comparing initiators of each of the three NOACs vs. warfarin in selected subgroups are shown in *Figure 4* (the HRs were additionally adjusted within each subgroup for variables for which balance was not achieved).

Baseline characteristics of patients with AF initiating NOACs or warfarin after *de novo* PS matching within each subgroup of initial NOAC dose are shown in Supplementary material online, *Tables S4 and S5*), while HRs for the primary endpoints for these analyses are shown in *Table 2*. The results for stroke/SE were in line with the main overall results. For bleeding, results of the initial dose analysis for dabigatran differed somewhat from the results for the overall population, with dabigatran lower dose having similar bleeding risks to warfarin (*Table 2*). The results of initial dose analyses for apixaban and rivaroxaban were consistent with the overall analyses.

The results of the primary endpoints when data from Denmark, Norway, and Sweden were analysed separately differed only slightly

Table 1 Baseline characteristics of three Scandinavian pooled and propensity score-matched NOAC vs. warfarin comparison cohorts

	Apixaban–warfarin cohort			Dabigatran–warfarin cohort			Rivaroxaban–warfarin cohort		
Characteristics	**Apixaban (*N* = 55 581)**	**Warfarin (*N* = 55 581)**	**SMD**	**Dabigatran (*N* = 28 428)**	**Warfarin (*N* = 28 428)**	**SMD**	**Rivaroxaban (*N* = 30 599)**	**Warfarin (*N* = 30 599)**	**SMD**
Female	24 440 (44.0%)	24 410 (43.9%)	0.001	11 300 (39.7%)	11 360 (40.0%)	0.004	13 420 (43.9%)	13 420 (43.8%)	0.000
Age, median (IQR)	75.1 (67.8–82.8)	75.1 (67.8–82.8)	0.004	71.7 (65.0–79.3)	71.7 (64.9–79.3)	0.002	74.6 (67.4–82.3)	74.7 (67.4–82.4)	0.004
<55 years	2840 (5.1%)	2740 (4.9%)	0.008	2220 (7.8%)	2230 (7.9%)	0.002	1550 (5.1%)	1520 (5.0%)	0.004
55 to <65 years	6850 (12.3%)	7010 (12.6%)	0.009	4920 (17.3%)	4970 (17.5%)	0.004	4010 (13.1%)	4060 (13.3%)	0.005
65 to <75 years	17 840 (32.1%)	17 790 (32.0%)	0.002	10 370 (36.5%)	10 290 (36.2%)	0.006	10 140 (33.1%)	10 030 (32.8%)	0.007
75 to <85 years	17 980 (32.3%)	17 860 (32.1%)	0.004	7810 (27.5%)	7800 (27.4%)	0.001	9620 (31.4%)	9650 (31.5%)	0.002
≥85 years	10 080 (18.1%)	10 170 (18.3%)	0.004	3110 (10.9%)	3140 (11.0%)	0.003	5290 (17.3%)	5340 (17.4%)	0.004
CCI group 0	22 000 (39.6%)	22 160 (39.9%)	0.006	13 490 (47.4%)	13 290 (46.8%)	0.014	12 670 (41.4%)	12 530 (40.9%)	0.009
CCI group 1–2	18 790 (33.8%)	18 290 (32.9%)	0.019	9540 (33.6%)	9390 (33.0%)	0.011	10 360 (33.8%)	10 020 (32.7%)	0.023
CCI group ≥3	14 800 (26.6%)	15 130 (27.2%)	0.014	5400 (19.0%)	5750 (20.2%)	0.031	7570 (24.7%)	8050 (26.3%)	0.036
Prior bleeding (any)	6110 (11.0%)	6050 (10.9%)	0.003	2630 (9.2%)	2660 (9.3%)	0.004	3250 (10.6%)	3320 (10.9%)	0.008
Prior intracranial bleeding	590 (1.1%)	570 (1.0%)	0.003	250 (0.9%)	270 (1.0%)	0.007	330 (1.1%)	330 (1.1%)	0.001
Prior stroke (any)	7200 (13.0%)	7190 (12.9%)	0.001	3110 (10.9%)	3150 (11.1%)	0.004	3910 (12.8%)	3980 (13.0%)	0.007
Prior ischaemic stroke	7000 (12.6%)	7000 (12.6%)	0.000	3040 (10.7%)	3070 (10.8%)	0.004	3800 (12.4%)	3870 (12.7%)	0.007
Chronic kidney disease	3170 (5.7%)	3210 (5.8%)	0.003	560 (2.0%)	610 (2.1%)	0.014	1280 (4.2%)	1420 (4.6%)	0.022
Heart failure	11 220 (20.2%)	11 270 (20.3%)	0.003	4240 (14.9%)	4280 (15.1%)	0.004	5480 (17.9%)	5540 (18.1%)	0.006
Coronary artery disease	13 040 (23.5%)	13 110 (23.6%)	0.003	5360 (18.9%)	5360 (18.9%)	0.000	6670 (21.8%)	6820 (22.3%)	0.012
Peripheral arterial disease	3840 (6.9%)	3930 (7.1%)	0.006	1580 (5.6%)	1620 (5.7%)	0.005	2080 (6.8%)	2160 (7.1%)	0.011
Hypertension	37 340 (67.2%)	37 410 (67.3%)	0.003	17 480 (61.5%)	17 390 (61.2%)	0.006	20 050 (65.5%)	20 130 (65.8%)	0.005
Diabetes	9520 (17.1%)	9570 (17.2%)	0.002	4070 (14.3%)	4070 (14.3%)	0.000	5050 (16.5%)	5150 (16.8%)	0.009
Chronic obstructive pulmonary disease	7020 (12.6%)	6970 (12.5%)	0.002	3080 (10.8%)	3140 (11.0%)	0.006	3820 (12.5%)	3890 (12.7%)	0.007
Liver disease	510 (0.9%)	530 (0.9%)	0.004	250 (0.9%)	260 (0.9%)	0.007	280 (0.9%)	310 (1.0%)	0.010
Alcoholism	1320 (2.4%)	1310 (2.4%)	0.001	760 (2.7%)	770 (2.7%)	0.002	790 (2.6%)	810 (2.7%)	0.004
Dementia	1110 (2.0%)	1050 (1.9%)	0.008	370 (1.3%)	370 (1.3%)	0.001	670 (2.2%)	650 (2.1%)	0.005

Table 1 (Continued).

Characteristics	Apixaban–warfarin cohort			Dabigatran–warfarin cohort			Rivaroxaban–warfarin cohort		
	Apixaban (*N* = 55 581)	Warfarin (*N* = 55 581)	SMD	Dabigatran (*N* = 28 428)	Warfarin (*N* = 28 428)	SMD	Rivaroxaban (*N* = 30 599)	Warfarin (*N* = 30 599)	SMD
Cancer 6 months before and including index date	1440 (2.6%)	1480 (2.7%)	0.005	840 (2.9%)	880 (3.1%)	0.009	1010 (3.3%)	1030 (3.4%)	0.002
Platelet inhibitors	21 020 (37.8%)	21 110 (38.0%)	0.003	9620 (33.9%)	9720 (34.2%)	0.007	11 610 (37.9%)	11 720 (38.3%)	0.008
Low-dose aspirin	18 430 (33.2%)	18 550 (33.4%)	0.005	8480 (29.8%)	8550 (30.1%)	0.005	10 090 (33.0%)	10 180 (33.3%)	0.006
ADP receptor blockers	4180 (7.5%)	4150 (7.5%)	0.002	1610 (5.7%)	1660 (5.8%)	0.007	2120 (6.9%)	2200 (7.2%)	0.010
Renin-angiotensin system inhibitors	26 110 (47.0%)	26 120 (47.0%)	0.000	12 070 (42.5%)	12 000 (42.2%)	0.005	13 640 (44.6%)	13 700 (44.8%)	0.003
Beta-blockers	40 010 (72.0%)	39 970 (71.9%)	0.002	19 730 (69.4%)	19 680 (69.2%)	0.004	20 820 (68.0%)	20 740 (67.8%)	0.005
Proton pump inhibitors	12 040 (21.7%)	12 040 (21.7%)	0.000	4950 (17.4%)	5010 (17.6%)	0.006	6320 (20.7%)	6350 (20.7%)	0.002
Non-steroidal anti-inflammatory drugs	4260 (7.7%)	4250 (7.6%)	0.001	2660 (9.3%)	2680 (9.4%)	0.003	2470 (8.1%)	2470 (8.1%)	0.000
Statins	19 250 (34.6%)	19 370 (34.9%)	0.004	9140 (32.2%)	9110 (32.0%)	0.002	10 410 (34.0%)	10 450 (34.2%)	0.003
Antidiabetic agents	6710 (12.1%)	6740 (12.1%)	0.002	2920 (10.3%)	2940 (10.3%)	0.002	3600 (11.8%)	3700 (12.1%)	0.010
Loop diuretics	13 760 (24.8%)	13 650 (24.5%)	0.005	5310 (18.7%)	5390 (19.0%)	0.008	6960 (22.8%)	7070 (23.1%)	0.008
Amiodarone	1480 (2.7%)	1520 (2.7%)	0.004	640 (2.2%)	650 (2.3%)	0.003	690 (2.2%)	700 (2.3%)	0.003
Dronedarone	450 (0.8%)	450 (0.8%)	0.001	100 (0.3%)	110 (0.4%)	0.006	140 (0.5%)	150 (0.5%)	0.001
Antihypertensive, combination drugs	5820 (10.5%)	5800 (10.4%)	0.001	3370 (11.9%)	3360 (11.8%)	0.001	3540 (11.6%)	3600 (11.8%)	0.007
Calcium channel blockers	13 390 (24.1%)	13 410 (24.1%)	0.001	6260 (22.0%)	6320 (22.2%)	0.005	7150 (23.4%)	7220 (23.6%)	0.005
Selective serotonin reuptake inhibitors	3460 (6.2%)	3450 (6.2%)	0.001	1440 (5.1%)	1470 (5.2%)	0.006	1890 (6.2%)	1870 (6.1%)	0.002
Drugs used in alcohol dependence	90 (0.2%)	80 (0.1%)	0.005	70 (0.2%)	60 (0.2%)	0.002	60 (0.2%)	60 (0.2%)	0.000
CHA_2DS_2-VASc, mean (SD)	3.4 (1.74)	3.4 (1.74)	0.001	2.9 (1.70)	2.9 (1.71)	0.002	3.3 (1.72)	3.3 (1.75)	0.011
CHA_2DS_2-VASc 0–1	8210 (14.8%)	8230 (14.8%)	0.001	6330 (22.3%)	6380 (22.4%)	0.004	4750 (15.5%)	4920 (16.1%)	0.015
CHA_2DS_2-VASc 2–3	22 050 (39.7%)	21 800 (39.2%)	0.009	12 510 (44.0%)	12 260 (43.1%)	0.018	12 800 (41.8%)	12 200 (39.9%)	0.040
CHA_2DS_2-VASc ≥4	25 320 (45.6%)	25 550 (46.0%)	0.008	9590 (33.7%)	9800 (34.5%)	0.015	13 050 (42.7%)	13 480 (44.1%)	0.028
HAS-BLED, mean (SD)	2.0 (1.04)	2.0 (1.04)	0.002	1.8 (1.07)	1.8 (1.08)	0.001	2.0 (1.04)	2.0 (1.07)	0.007
HAS-BLED < 3	40 000 (72.0%)	40 050 (72.1%)	0.002	21 260 (74.8%)	21 110 (74.3%)	0.012	21 890 (71.5%)	21 520 (70.3%)	0.027
HAS-BLED ≥ 3	15 580 (28.0%)	15 530 (27.9%)	0.002	7170 (25.2%)	7320 (25.7%)	0.012	8710 (28.5%)	9080 (29.7%)	0.027

ADP, adenosine diphosphate; CCI, Charlson comorbidity index; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke or transient ischaemic attack, vascular disease, age 65–74 years, sex category; HAS-BLED, hypertension, abnormal renal or liver function, stroke, bleeding, labile INR, elderly, drug or alcohol usage; IQR, interquartile range; and SMD, standardized mean difference. To comply with data protection regulation of Statistics Denmark, numbers of events or patients in subgroups were rounded to the nearest 10.

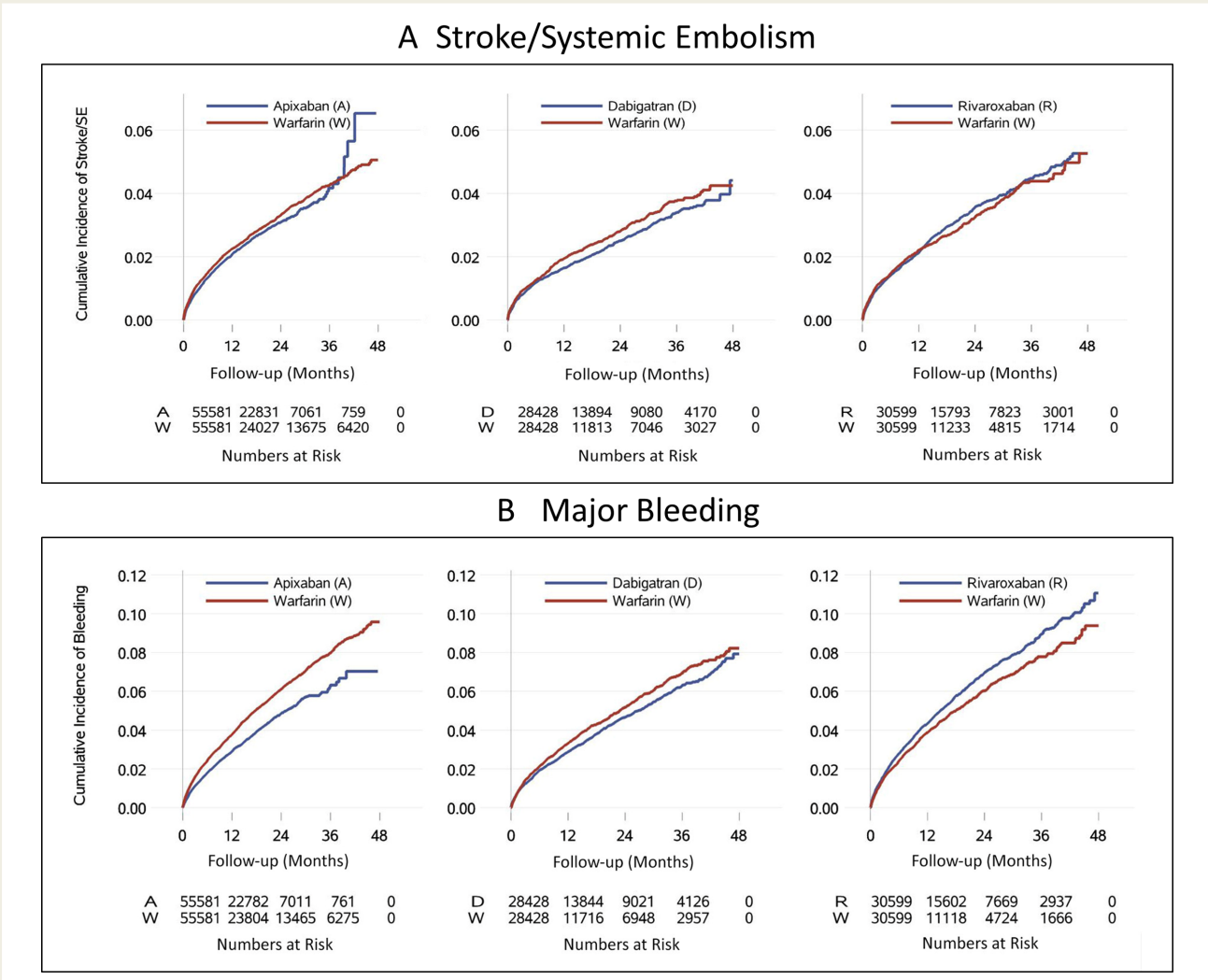


Figure 2 Cumulative incidence of stroke/systemic embolism (*A*) and major bleeding (*B*) in the three propensity score-matched comparison cohorts from Scandinavia. SE, systemic embolism.

from the results for all countries combined (Supplementary material online, *Figure S1*).

Sensitivity analyses

The three sensitivity analyses performed for the primary endpoints were generally consistent with the primary analyses (Supplementary material online, *Table S6*).

Discussion

In this large Scandinavian study among AF patients initiating oral anticoagulation, dabigatran, apixaban, and rivaroxaban had similar rates of stroke/SE to patients initiating warfarin. Rates of major bleeding were lower with apixaban and dabigatran and higher with rivaroxaban, each compared with warfarin. The NOACs were associated with a lower rate of intracranial bleeding, but both dabigatran and rivaroxaban were associated with a higher risk of gastrointestinal bleeding compared with warfarin. Given the pairwise matching of each NOAC vs. warfarin, this study does not provide evidence of comparative safety or effectiveness among the NOACs. The lower intracranial bleeding risk appears to be a NOAC class effect, as shown both in RCTs and in real-world populations.[4,5,6,38]

To the best of our knowledge, this is one of the largest observational studies to date on NOACs and warfarin in patients with AF, with inclusion of almost 220 000 OAC-naïve patients from Scandinavia (~140 000 NOAC patients). Due to the high-quality nationwide registries, person-level linkage between registries, and complete follow-up, Scandinavian countries are an optimal setting to address comparative effectiveness and safety of anticoagulants in routine clinical practice. Other strengths include universal access to healthcare, similar clinical practice, as well as uniform recording practices, comparable patterns of hospitalization and referral to specialist care, and high quality of warfarin therapy.[33–35] Furthermore, uptake of NOACs in the Scandinavian countries has been high.[36,37]

The results of our study are generally consistent with previous observational studies and meta-analyses, showing that in routine clinical use, NOACs are associated with comparable rates of

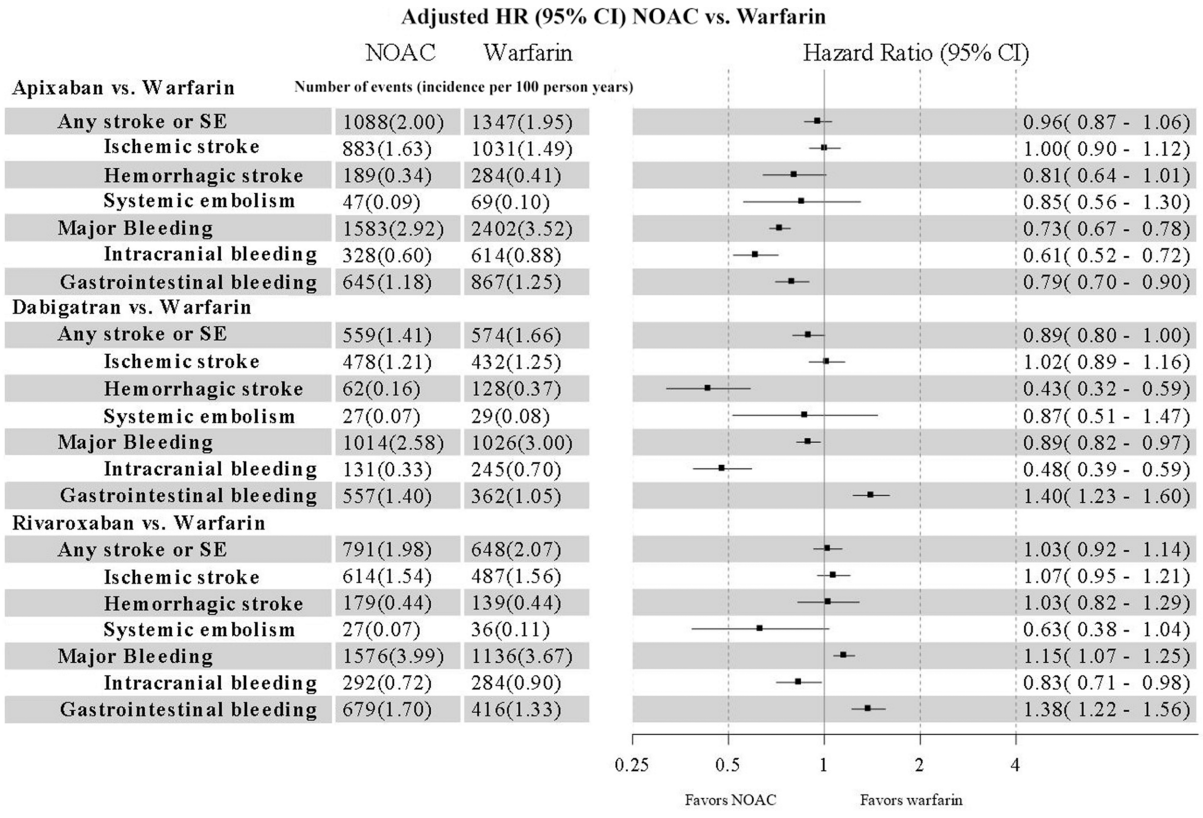


Figure 3 Hazard ratios of primary and selected secondary endpoints in the three propensity score-matched comparison cohorts from Scandinavia. NOAC, non-vitamin K antagonist oral anticoagulant; and CI, confidence interval.

stroke/SE compared with warfarin, similar or lower rates of major bleeding, and lower rates of intracranial bleeding.[9,20,38] Most previous, but smaller, cohort studies comparing NOACs vs. warfarin or NOACs vs. NOACs from Scandinavian countries showed similar results.[10,12,39,40] However, in the largest study to date, the ARISTOPHANES study,[11] pooling Centers for Medicare & Medicaid Services Medicare data and four US commercial claims databases, dabigatran, rivaroxaban, and apixaban were all associated with lower rates of stroke/SE compared with warfarin. Contrary to the ARISTOPHANES study, we did not find reductions in the risk of stroke/SE with NOACs in our study. A number of factors may have contributed to differences between the results of the ARISTOPHANES study and our own study, including differences in data sources, patient characteristics, and clinical practice. In particular, better warfarin control in the Scandinavian countries leading to better warfarin effectiveness might have influenced the results. At the same time, both apixaban and dabigatran were associated with lower rates of major bleeding compared with warfarin in both the ARISTOPHANES study and our study. These observations are consistent also with most previous studies, from both Scandinavia[19] and the USA.[9] Moreover, although the present study did not PS match NOAC cohorts for comparative effectiveness assessment across the NOACs, the observed trends regarding major bleeding generally align with a large Norwegian cohort study that compared safety and effectiveness among NOACs. Rutherford *et al.* found that rivaroxaban was associated with a higher risk of major bleeding than apixaban or dabigatran.[41]

Our estimates for the primary endpoints were robust to changes in analytical approaches. Since the registries lack information on warfarin dosage and INR, the calculation of warfarin days of supply was not straightforward. The consistency of results, irrespective of the method for calculation of warfarin days of supply as well as in the ITT analysis, is reassuring.

In the primary analyses, patients initiating standard as well as reduced doses were analysed together. In one subgroup analysis, we studied patients initiating standard and reduced doses separately after *de novo* PS matching within the cohorts based on initial dosing. The results were comparable to the overall results with respect to stroke/SE for both doses for all three NOACs compared with warfarin. For dabigatran, while the overall results were suggestive of possible reduction in stroke, this was not seen when looking at the per-dose analysis. This leads to our conclusion that the rates of stroke/SE for dabigatran and warfarin are similar. The risk of major bleeding with apixaban compared with warfarin was lower for both doses. For rivaroxaban, the results for major bleeding for both standard and lower doses were consistent with the

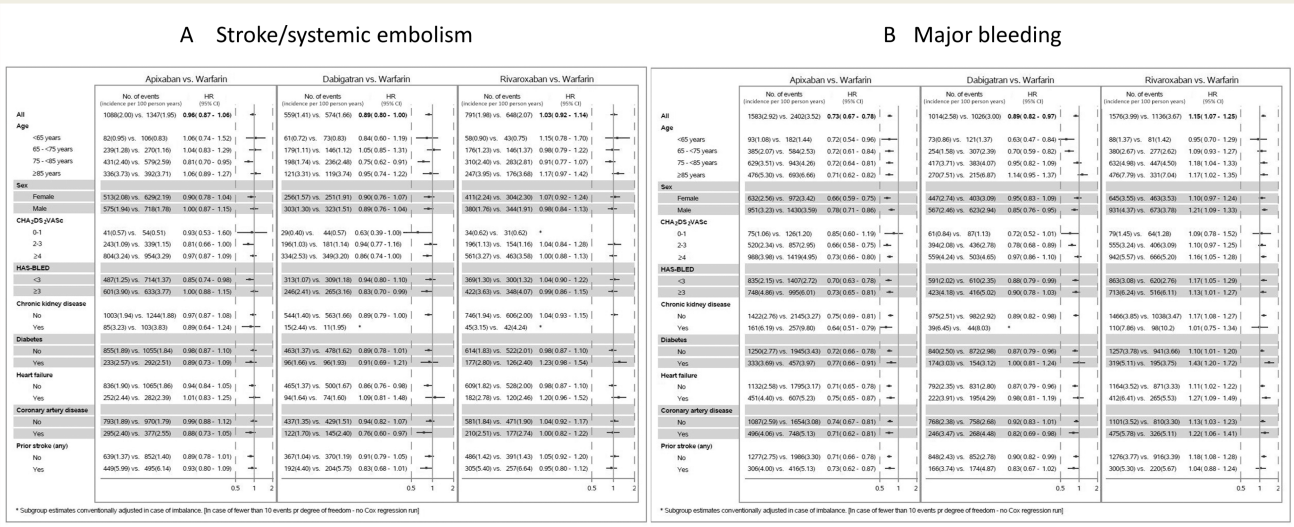


Figure 4 Risks of stroke/systemic embolism (*A*) and major bleeding (*B*) in subgroups of the three propensity score-matched comparison cohorts from Scandinavia. CI, confidence interval.

Table 2 Primary endpoint hazard ratios, stratified on initial dose after *de novo* PS matching within initial NOAC dose subgroups among Scandinavian NOAC vs. warfarin cohorts

Dose	Successfully matched NOAC initiators/total NOAC initiators (%)	Maximum SMD before matching/after matching	Hazard ratio (95% CI) after *de novo* PS matching within each subgroup of initial NOAC dose	
			Stroke/SE	Major bleeding
Apixaban vs. warfarin				
Standard dose	42 672/50 310 (85%)	0.29/0.02	0.88 (0.78–1.00)	0.75 (0.69–0.83)
Reduced dose	18 794/21 275 (88%)	1.07/0.02	0.96 (0.83–1.10)	0.69 (0.61–0.76)
Dabigatran vs. warfarin				
Standard dose	18 701/20 478 (91%)	0.78/0.03	0.95 (0.80–1.12)	0.75 (0.66–0.85)
Reduced dose	10 669/10 731 (99%)	0.62/0.03	0.90 (0.76–1.05)	0.95 (0.85–1.07)
Rivaroxaban vs. warfarin				
Standard dose	23 703/28 366 (84%)	0.62/0.04	0.96 (0.85–1.09)	1.09 (0.99–1.20)
Reduced dose	9088/9214 (99%)	0.74/0.04	0.98 (0.83–1.16)	1.15 (1.02–1.29)

CI, confidence interval; NOAC, non-vitamin K antagonist oral anticoagulant; PS, propensity score; SE, systemic embolism; and SMD, standardized mean difference.

overall results, indicating an increased risk of major bleeding. For dabigatran, the standard dose was associated with a clinically relevant reduction in bleeding risk, which was not the case for the reduced dose. We speculate that these findings are at least partially attributable to unmeasured confounding. The available data sources do not contain information on dose appropriateness or on the actual prescribed dose. Evaluation of the appropriateness of the dose prescribed (standard or reduced dose of NOAC) requires knowledge of age, serum creatinine, and body weight. The variables of serum creatinine and body weight are not available in the nationwide registries in Scandinavia.[19] Although we were unable to identify users of NOACs per label regarding dose, we attempted to compensate for this with *de novo* PS estimation and matching within dosage groups as inferred from tablet strength in the initial dispensing.

Limitations

Patients initiating apixaban and warfarin were older and had more comorbidities than patients initiating dabigatran or rivaroxaban. Although PS matching was performed, residual confounding cannot be ruled out. Selection of the NOACs during the study period was based on physician preference, potentially favouring warfarin and apixaban for older and more ill patients based on real-world evidence; other unmeasured factors could influence prescribing. Furthermore, comparisons of NOAC vs. warfarin are not

interpretable as head-to-head NOAC vs. NOAC comparisons, as each pairwise NOAC vs. warfarin matched cohort had different characteristics. Misclassification of treatment status by dispensing records or interruptions during hospital stays or misclassification of OAC treatment-naïve status by a 12-month washout period might have occurred. If non-differential, it is expected to result in underestimation of any true effect. At the same time, definitions of the outcomes were designed to maximize specificity and are therefore not expected to bias the HRs.

The results from the cumulative incidence functions (Supplementary material online, *Figure S2*) suggest some inherent uncertainty in the apixaban data after ~36 months where the numbers at risk are low. It is hypothesized that this may have been due to the later reimbursement of apixaban in these countries resulting in fewer patients with follow-up >36 months. The daily dose of warfarin was only a crude estimate because no information on the quality of warfarin treatment control or dose for individual patients was available.

Calendar year was included in the computation of the dabigatran–warfarin and rivaroxaban–warfarin PS matches but was not included in the computation of apixaban–warfarin PS matches (as it would result in a substantial depletion of the PS-matched population). Instead, calendar year was used as an adjustment variable in the regression model. We studied patients with AF in the absence of mechanical valves or mitral stenosis. Therefore, results are not generalizable to patients with AF and mechanical valves or mitral stenosis. Finally, this study focused on OAC initiators with a hospital diagnosis of AF, and the results are not necessarily generalizable to patients who are not OAC-naïve or to those treated exclusively in primary care. Our analysis covers patients treated through 2016 and is thus subject to earlier versions of the AF treatment guidelines,[1,42] which have since been updated.[3]

Conclusions

In this Scandinavian cohort study of OAC-naïve patients with AF, dabigatran, rivaroxaban, and apixaban were associated with comparable rates of stroke and/or SE compared with warfarin. Apixaban and dabigatran were associated with lower rates of bleeding compared with warfarin, while rivaroxaban was associated with higher rates of bleeding compared with warfarin. These findings can help inform physicians and patients to choose the optimal treatment for stroke prevention in patients with AF.

Supplementary material

Supplementary material is available at *European Heart Journal—Quality of Care and Clinical Outcomes* online.

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Data availability

The data underlying this article cannot be shared for privacy reasons and according to local laws and regulations. Any further inquiries regarding data availability should be directed to Professor Vera Ehrenstein (ve@clin.au.dk).

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