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Contemporary findings in real-life Danish patients

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Major Bleeding Complications and Persistence With Oral Anticoagulation in Non-Valvular Atrial Fibrillation: Contemporary Findings in Real-Life Danish Patients

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***Background*—**The nonvitamin K antagonist oral anticoagulants have recently become available as an alternative to warfarin as stroke prophylaxis in atrial fibrillation, but data on real-life patient experience, including bleeding risk, are lacking. Our objective was to compare major bleeding events and nonpersistence between the nonvitamin K antagonist oral anticoagulant apixaban and other nonvitamin K antagonist oral anticoagulants (dabigatran and rivaroxaban) and warfarin in a contemporary, nation-wide cohort of patients with nonvalvular atrial fibrillation.

***Methods and Results*—**Of 54 321 patients (median age, 73 years; 56% male; mean CHA_2DS_2-VASc score, 2.9), 7963, 6715, 15 413, and 24 230 patients initiated apixaban, rivaroxaban, dabigatran, and warfarin, respectively. Apixaban and rivaroxaban initiators were older, less often male, with higher HAS-BLED and CHA_2DS_2-VASc scores compared with dabigatran and warfarin initiators. A total of 2418 patients (4.5%) experienced a major bleeding event over all available follow-up. In this period, rivaroxaban (hazard ratio [HR] [95% CI], 1.49 [1.27–1.77]), dabigatran (HR, 1.17 [1.00–1.38]), and warfarin (HR, 1.23 [1.05–1.43]) users were significantly more likely to bleed than apixaban users. Findings were similar when restricted to the first 30 days after OAC initiation. Risk of nonpersistence was higher for dabigatran (HR, 1.45 [1.33–1.59]) and warfarin initiators (HR, 1.22 [1.12–1.33]), but not for rivaroxaban initiators (HR, 1.07 [0.96–1.20]) compared with apixaban initiators.

***Conclusions*—**In a real-world cohort of nonvalvular atrial fibrillation patients, apixaban had a lower adjusted major bleeding risk compared with rivaroxaban, dabigatran, and warfarin. Apixaban had a lower risk of nonpersistence compared with dabigatran and warfarin and similar risk compared with rivaroxaban. **(*J Am Heart Assoc*. 2017;6:e004517. DOI: 10.1161/JAHA.116.004517.)**

Key Words: anticoagulant • atrial fibrillation • bleeding

Nonvitamin K antagonist oral anticoagulants (NOACs) may have a large impact on standard stroke prevention and management in atrial fibrillation (AF). Predictable pharmacodynamics and kinetics with fewer drug-drug and drug-food interactions compared with warfarin may simplify their use for health care professionals and patients. Several major trials have shown on-par or better efficacy and safety compared with warfarin.[1–3] In these trials, apixaban and low-dose dabigatran had lower risk of major bleeding compared with warfarin, whereas the risk was similar for rivaroxaban and high-dose dabigatran against warfarin. Despite considerable interest in the NOACs in recent years, data about their use and performance in real-life clinical care are limited. In particular, there is a need for safety data looking at any differences in bleeding risk and persistence between NOACs in routine care. Also, whereas previous studies suggest an initially increased bleeding risk with use of warfarin, it is unknown whether this should be a concern when initiating an NOAC.[4]

European and American guidelines now support NOACs as an option in first-line oral anticoagulant (OAC) therapy for patients with nonvalvular AF with 1 or more stroke risk factors.[5,6] However, transition from randomized evidence to actual clinical practice is key to optimize the management of

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OAC drug use in patients with AF. Data from Danish administrative registries provide comprehensive data on actual clinical practice and patient outcomes. We therefore aimed to assess and compare shorter-term (within 30 days) and longer-term major bleeding events and persistence comparing apixaban, rivaroxaban, dabigatran, and warfarin using Danish data sets.

Methods

Registries

From nation-wide administrative registries, we extracted information on hospitalizations, vital status, and pharmacological treatment for each patient using a personal and unique identifier.[7] The National Patient Registry contains information on hospital discharge codes with both primary and secondary diagnoses. Diagnoses are recorded by the International Classification of Diseases (ICD) 8th (until 1994) and 10th revisions (from 1995 and onward). The registry also holds information on surgical procedures according to the NOMESCO classification.[7] The National Prescription Registry includes information on prescription drugs in terms of strength, number of tablets, and date of prescription according to Anatomical Therapeutical Classification codes.[8] The Civil Personal Registry holds information on vital status, sex, and age.[9] We use cross-linkage through secured servers to link patients, hospitalization diagnoses, and prescription information at the individual level over time. All registries included information up to December 31, 2015. Codes used are in Table 1.

Study Population and OAC Treatment

We identified all patients aged 18 years or older with a history of nonvalvular AF and grouped them into 4 cohorts according to the first OAC (apixaban, rivaroxaban, dabigatran, and warfarin) initiated in the study period (August 22, 2011 to December 31, 2015; Figure 1). We defined new initiation as no OAC prescription 6 months before inclusion; hence, the population consisted of "naïve" OAC users.[10] Date of first prescription claim defined the date of inclusion. We only included dosages recommended and approved by the Danish Health and Medicines Authority for thromboprophylaxis in AF (apixaban 2.5 and 5 mg twice-daily [BID; approved December 10, 2012], dabigatran 110 and 150 mg BID [approved August 22, 2011], and rivaroxaban 15 and 20 mg once-daily (OD; approved February 6, 2012]). We excluded patients with recent (<6 months) venous thromboembolism or pulmonary embolism or recent (<5 weeks) hip or knee prosthetic implantation surgery to ensure patients received OAC treatment for AF.

We defined exposure periods to the different OAC treatments during follow-up using all prescription claims during the study period. Patients were considered exposed to a specific OAC when tablets were available for consumption. The algorithm to calculate this, as previously published, uses the date, number, and strength of tablets claimed for each individual from the national prescription registry.[11] If hospitalization occurs, no consumption of tablets was recorded given that hospitals deliver medication during hospital stays. Exposure to more than 1 OAC was not allowed, so any subsequent prescription claim for a different OAC defined treatment switch. Patients could stop or switch OAC treatment during follow-up according to availability of tablets (for definition of duration of exposure, please see below). The NOAC, edoxaban, was not available in Denmark in the study period.

Comorbidity and Concomitant Pharmacotherapy

Stroke risk factors comprising the CHA_2DS_2-VASc (congestive heart failure, hypertension, age >75 years, diabetes mellitus, stroke/transitional cerebral ischemia, vascular disease, age 65–74 year, or female sex) score were defined from the registries as previously published.[12] The score has been shown to accurately predict risk of stroke in a similar population with AF. Bleeding risk factors comprising a modified HAS-BLED (hypertension, abnormal renal or liver function, stroke, bleeding, labile international normalized ratio [INR], elderly [>65 years], drugs [nonsteroidal anti-inflammatory drug {NSAID}, antiplatelets, alcohol]) score were defined in a similar manner.[13] Labile INR was not included because INR values were not available. Antiplatelet treatment at baseline was defined by prescription of either aspirin and nonaspirin (ie, clopidogrel, ticagrelor, and prasugrel) antiplatelet agents in the 6 months preceding inclusion.

Major Bleeding Complications

We defined major bleeding events as first hospitalization associated with a code for bleeding and reported bleeding overall and by site, including gastrointestinal and intracranial bleedings (Table 1). This definition includes all relevant thrombolysis in myocardial infarction major bleeds[14] and has been used previously.[11] We examined first bleeding events during the full follow-up time available in the registries ("total bleeding") and also restricted to the first 30 days after OAC initiation ("30-day bleeding").

Persistence

We defined nonpersistence as no claim for the same as well as for any OAC for at least 30 days following the end of last

Table 1. Codes Used

	ICD/ATC/NOMESCO Codes	Comment
Inclusion criteria		
AF	Presence of: ICD8: 42793, 42794. ICD10: I48. Absence of: ICD8: 4240, 4241, 39500–39502, 39508, 39509, 39600–39604, 39608, 39609. ICD10: I05, I06, I080A, I081A, I082A, I083A, Z952, Z954. NCSP: KFKD, KFKH, KFMD, KFMH, KFGE, KFJF	Defined from diagnosis of AF with the absence of diagnosis codes of valvular AF and mitral or aortic valve surgery
OAC treatment	ATC: B01AA03, B01AE07, B01AF01, B01AF02	Includes use of warfarin, apixaban, rivaroxaban, and dabigatran
Exclusion criteria		
Recent venous thromboembolism	ICD-10: I801–3, I808–9, I821–3, I8289	
Recent orthopedic surgery	NOMESCO: KNFB, KNFC, KNGB, KNGC	
Outcome		
Major bleeding	ICD-10: D62, I60, I61, I62, R31, R04, D500, H313, H356, H431, H450, I312, I850, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K625, K661, K920, K921, K922, S064, S065, S066, J942, K228F, K298A, K638B, K638C, K838F, K868G, I864A, H052A, S368D, G951A	Defined from diagnosis of intracranial bleeding, major gastrointestinal bleeding, respiratory, renal/urinary tract, ocular, retroperitoneal or pericardial bleeding, and bleeding attributed to anemia. Only bleedings requiring hospitalization were used
Comorbidity/medication		
Hypertension	ATC: C02A, C02B, C02C, C02L, C03A, C03B, C03D, C03E, C03X, C07B, C07C, C07D, C08G, C02DA, C09BA, C09DA, C02DB, C02DD, C02DG, C07A, C07B, C07C, C07D, C07F, C08, C09BB, C09DB, C09AA, C09BA, C09BB, C09CA, C09DA, C09DB, C09XA02, C09XA52	Defined from combination treatment with at least 2 classes of antihypertensive drugs: adrenergic α-antagonists, nonloop diuretics, vasodilators, beta-blockers, calcium-channel blockers, and renin-angiotension system inhibitors
Stroke	ICD-10: DI63, DI64, DI74, G458, G459	Includes transient ischemic attack
Vascular disease	ICD-10: I21, I22, I700, I702, I703, I704, I705, I706, I707, I708, I709	Includes myocardial infarction and peripheral artery disease
Chronic kidney disease	ICD-10: N02, N03, N04, N05, N06, N07, N08, N11, N12, N14, N18, N19, N26, N158, N159, N160, N162, N163, N164, N168, Q612, Q613, Q615, Q619, E102, E112, E132, E142, I120, M300, M313, M319, M321B	Defined from diagnosis of chronic glomerulonephritis, chronic tubulointestinal nephropathy, diabetic, and hypertensive nephropathy among others
Liver disease	ICD-10: B15, B16, B17, B18, B19, C22, K70, K71, K72, K73, K74, K75, K76, K77, Z944, I982, D684C, Q618A	Defined from diagnosis of liver chronic liver disease, cirrhosis, and hepatitis
Alcohol abuse	ICD-10: F10, K70, E52, T51, K860, E244, G312, I426, O354, Z714, Z721, G621, G721, K292, L278A, ATC: N07BB	Defined from alcohol-related diagnosis codes or at least 1 dispensed prescription of an alcohol antagonist drug used to treat chronic alcoholism
Bleeding	ICD-10: D62, I60, I61, I62, R31, R04, D500, H313, H356, H431, H450, I312, I850, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K625, K661, K920, K921, K922, S064, S065, S066, J942, K228F, K298A, K638B, K638C, K838F, K868G, I864A, H052A, S368D, G951A	
Heart failure	ICD10: I42, I50, I110, J81	
Diabetes mellitus	ATC: A10	Codes for glucose-lowering medication
Aspirin	ATC: B01AC06, N02BA01	
Nonaspirin antiplatelets	ATC: B01AC22, B01AC24, B01AC04	Includes clopidogrel, prasugrel, ticagrelor
NSAID	ATC: M01A	Excludes glucosamin (M01AX05)

AF indicates atrial fibrillation; ICD, International Classification of Diseases; NSAID, nonsteroidal anti-inflammatory drug; OAC, Oral anticoagulant.

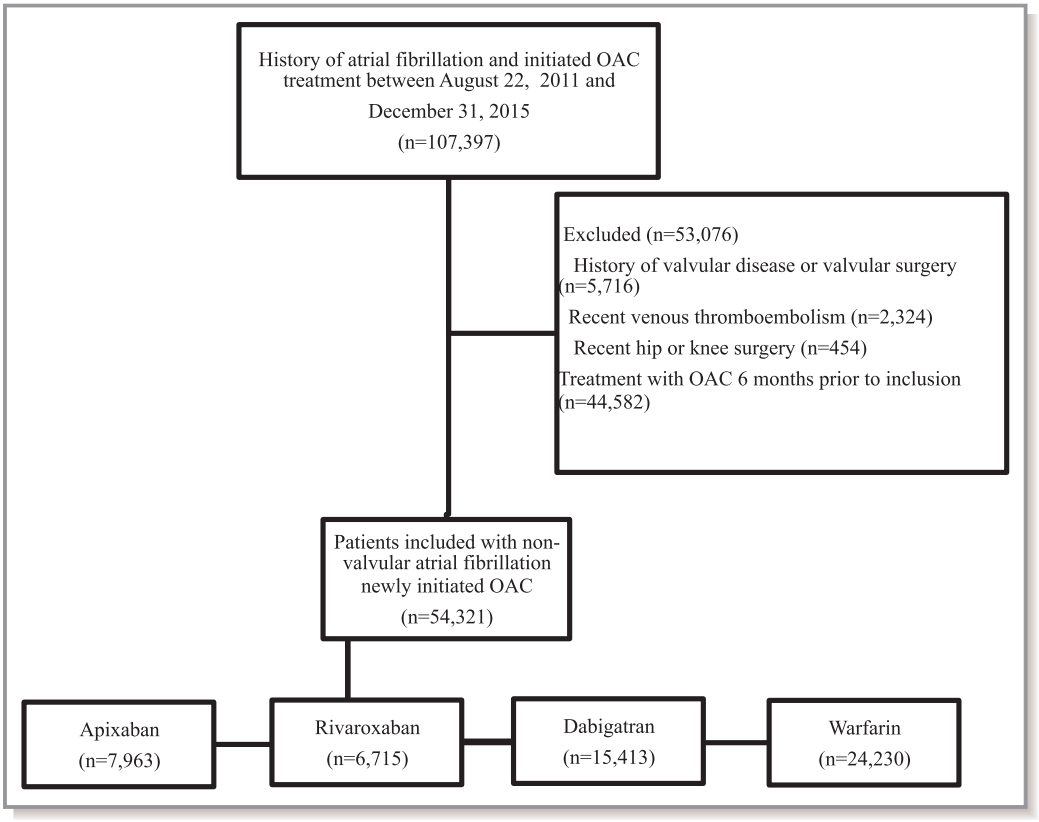

Figure 1. Overview of the study population. OAC indicates oral anticoagulant.

OAC treatment period (ie, a treatment gap of more than 30 days).

Statistical Analyses

For baseline characteristics, we described continuous variables by the mean and SD or median and interquartile range (IQR). For the persistence analyses, we calculated the duration of each OAC treatment period as the time from inclusion date to nonpersistence date as defined above (of note and as described above—switch of treatment before date of nonpersistence was allowed). For the bleeding analyses, we calculated the duration from inclusion date to first bleeding event, censoring at date of nonpersistence. For both sets of analyses, we also censored at date of claim for more than 1 OAC drug (because there is no valid indication for more than 1 concurrent OAC), death, and end of study. Figure 2 illustrates allocation of major bleeding and nonpersistence outcome and switch of treatment according to OAC exposure.

We estimated risk of major bleeding and of nonpersistence by Cox regression models adjusted for age, sex, calendar year, variables in the CHA_2DS_2-VASc and HAS-BLED scores, and switch of OAC treatment. For all analyses, apixaban was used as reference. For the primary outcomes, additional analyses using warfarin as reference were conducted. We calculated cumulative incidences of major bleeding and nonpersistence (accounting for competing risks of death and switching OAC) for the first 3 years of follow-up. Because of the time-varying OAC exposure, we only reported cumulative incidence for patients' first OAC.

The only clinically relevant interactions found was sex, so we undertook additional stratified analyses of major bleeding (P for interaction, 0.0016) and nonpersistence (P for interaction, <0.0001) by sex. For the nonpersistence outcome, the initial risk would differ between warfarin/rivaroxaban and apixaban/dabigatran, because typical warfarin and rivaroxaban pack sizes last for 100 days, whereas shorter for apixaban (50 days) and dabigatran (30 days), that is, the initial length of exposure differed between OAC. Hence, we performed a landmark analysis at the 90-day mark. No other violation of model assumptions was found.

We ran the following preplanned, supplemental analyses: (1) stratified dabigatran use by 110 and 150 mg BID patients including an analysis for patients under the age of 80 years only (ie, excluding patients where 150 mg of BID is not indicated), given that different dosages were investigated separately in the RE-LY trial; (2) major bleeding complications and nonpersistence from when all NOACs were available (January 1, 2013 [Defined data of "Debut apixaban"]) to minimize selection bias caused by change of NOAC availability during follow-up; and (3) stratification by to patients who

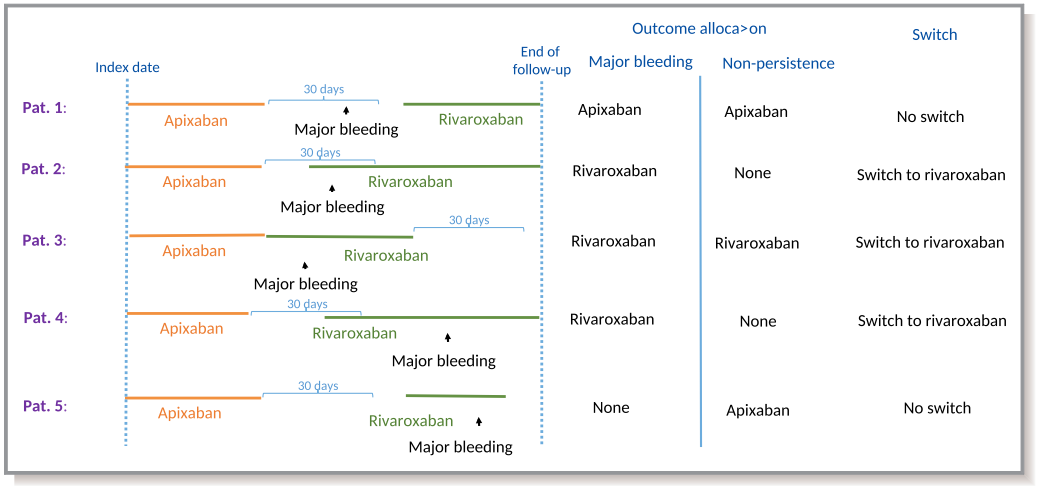

Figure 2. Examples of allocation of major bleeding and nonpersistence outcome and switch of treatment according to OAC exposure. OAC indicates oral anticoagulant.

did and who did not switch between OAC drugs given that switchers may be a different population from nonswitchers.

All analyses used the SAS statistical package (version 9.4; SAS Institute Inc., Cary, NC) and R (version 4.1; R Foundation for Statistical Computing).

Ethics

This study was approved by the Danish Data Protection Agency (reference no. 2007-58-0015; internal reference: GEH-2014-013 I-suite no. 02731). Information was made available to us by encrypted data access with anonymization of patients so that no individuals could be identified. By Danish law, retrospective studies do not require ethical committee approval.

Results

Population and Follow-up

We identified 54 321 patients with nonvalvular AF who initiated OAC treatment. Median age was 73 years (IQR, 66–81), 56% were male, and mean CHA_2DS_2-VASc and HAS-BLED scores were 2.9 (SD, 1.6) and 2.2 (SD, 1.2), respectively. Mean follow-up time per patient was 403 days and total patient-time at-risk was 67 764 person-years. Patient characteristics by OAC initiated are in Table 2. Patients initiating apixaban and rivaroxaban were older and less often male, with higher CHA_2DS_2-VASc scores, compared with dabigatran or warfarin users. According to year of inclusion, apixaban and rivaroxaban initiation was more frequent at the end of the study period whereas dabigatran and warfarin initiation declined. Characteristics of dabigatran 110 and 150 mg BID initiators are in Table 3. Dabigatran 110 mg BID users were considerably older (mean age, 80.1 vs 65.6 years) with higher mean HAS-BLED score (2.5 vs 1.8) compared to dabigatran 150 mg BID users. Among warfarin initiators, 11.4% (n=2752) subsequently switched to an NOAC (564 to apixaban, 758 to rivaroxaban, and 1430 to dabigatran, comprising 20.5%, 27.5%, and 52.0%, respectively). Among initiators of an NOAC, 9.4% (n=2070) subsequently switched to warfarin. Switchers between specific OAC treatments are shown in Table 4. Mean follow-up time ranged from 268 to 511 days between OAC groups (Table 5).

Major Bleeding Complications

Of all included patients, 4.5% (2418) experienced a major bleeding event during total follow-up. Most common bleeding sites were gastrointestinal, renal, and intracranial (Table 6). Crude incidence rates during follow-up were 3.6 (252 events), 4.3 (343 events), 2.9 (695 events), and 3.9 (1128 events) per 100 person-years for apixaban, rivaroxaban, dabigatran, and warfarin, respectively. Figure 3 shows cumulative incidences of major bleeding event by OAC initiated. Table 5 shows adjusted risk of total and 30-day major bleeding for the different OAC groups. Compared with apixaban, rivaroxaban, dabigatran, and warfarin were all associated with increased total and 30-day major bleeding risk. Compared with warfarin, rivaroxaban was associated with a higher and apixaban with a lower total major bleeding risk (hazard ratio [HR], 0.82 [0.70–0.95]); dabigatran had a similar total major bleeding risk to warfarin. The 30-day major bleeding risk was lower for apixaban (HR, 0.71 [0.51–0.99]) compared to warfarin and comparable for rivaroxaban (HR, 1.20 [0.90–1.60]) and dabigatran (HR, 1.17 [0.93–1.47]). In the sex-stratified analyses (Table 7), there was an increased total major bleeding risk versus apixaban for rivaroxaban, but not for dabigatran or warfarin, among men. There was an increased total major bleeding risk for all OACs versus apixaban among women.

Table 2. Characteristics of the Study Population

	Apixaban	Rivaroxaban	Dabigatran	Warfarin
No. of patients	7963	6715	15 413	24 230
Low dosage (%)/high dosage (%)	3010 (37.8)/4953 (62.2)	1840 (27.4)/4875 (72.6)	6234 (40.4)/9179 (59.6)	N/A
Age, median [IQR]	76 [68, 84]	74 [67, 83]	71 [65, 79]	73 [65, 80]
Age, mean (SD)	75.4 (11.10)	74.4 (11.0)	71.5 (11.0)	72.1 (11.3)
Male sex (%)	4049 (50.8)	3490 (52.0)	8740 (56.7)	14 159 (58.4)
Year of inclusion (%)				
2011	—	—	1465 (9.5)	4481 (18.5)
2012	—	447 (6.7)	4506 (29.2)	6658 (27.5)
2013	632 (7.9)	1737 (25.9)	4596 (29.8)	5358 (22.1)
2014	2794 (35.1)	1662 (24.8)	3608 (23.4)	4263 (17.6)
2015	4537 (57.0)	2869 (42.7)	1238 (8.0)	3470 (14.3)
CHA_2DS_2-VASc score, mean (SD)	3.15 (1.62)	3.02 (1.62)	2.73 (1.60)	2.91 (1.66)
CHA_2DS_2-VASc score, median [IQR]	3 [2, 4]	3 [2, 4]	3 [2, 4]	3 [2, 4]
CHA_2DS_2-VASc score (%)				
Low (score 0)	353 (4.4)	294 (4.4)	1162 (7.5)	1675 (6.9)
Intermediate (score 1)	923 (11.6)	938 (14.0)	2451 (15.9)	3363 (13.9)
High (score >1)	6687 (84.0)	5483 (81.7)	11 800 (76.6)	19 192 (79.2)
HAS-BLED score, mean (SD)	2.25 (1.20)	2.21 (1.16)	2.05 (1.17)	2.18 (1.22)
HAS-BLED score, median [IQR]	2 [1, 3]	2 [1, 3]	2 [1, 3]	2 [1, 3]
HAS-BLED score (%)				
Low (score 0–1)	2273 (28.5)	1944 (29.0)	5115 (33.2)	7312 (30.2)
Intermediate (score 2)	2404 (30.2)	2129 (31.7)	4863 (31.6)	7178 (29.6)
High (score >2)	3286 (41.3)	2642 (39.3)	5435 (35.3)	9740 (40.2)
Stroke (%)	1692 (21.2)	1228 (18.3)	2451 (15.9)	3597 (14.8)
Vascular disease (%)	828 (10.4)	619 (9.2)	1426 (9.3)	3343 (13.8)
Liver disease (%)	115 (1.4)	88 (1.3)	166 (1.1)	390 (1.6)
Heart failure (%)	1362 (17.1)	1120 (16.7)	2442 (15.8)	5128 (21.2)
Diabetes mellitus (%)	1031 (12.9)	830 (12.4)	1785 (11.6)	3354 (13.8)
Hypertension (%)	3463 (43.5)	3092 (46.0)	6907 (44.8)	11 699 (48.3)
Kidney disease (%)	391 (4.9)	276 (4.1)	330 (2.1)	1860 (7.7)
Bleeding (%)	1159 (14.6)	811 (12.1)	1816 (11.8)	3261 (13.5)
Alcohol misuse (%)	287 (3.6)	227 (3.4)	522 (3.4)	753 (3.1)
Nonaspirin antiplatelets (%)	917 (11.5)	690 (10.3)	1274 (8.3)	2173 (9.0)
Aspirin antiplatelet (%)	2982 (37.4)	2697 (40.2)	6212 (40.3)	10 267 (42.4)
NSAIDs (%)	1119 (14.1)	951 (14.2)	2279 (14.8)	3379 (13.9)

IQR indicates interquartile range; N/A, not applicable; NSAIDs, nonsteroidal anti-inflammatory drugs.

Nonpersistence

Of all included patients, 14 800 (27.2%) experienced a break of at least 30 days during follow-up. Figure 4 shows the cumulative incidence of nonpersistence by OAC initiated for patients who did not switch OAC. After ≈3 years, 15% of apixaban and rivaroxaban, 30% of dabigatran, and 60% of warfarin patients were nonpersistent. In the adjusted analyses with apixaban as reference, dabigatran or warfarin initiators were more likely to be nonpersistent whereas rivaroxaban initiators had similar risk (Table 5). In the adjusted analyses with warfarin as reference, apixaban (HR, 0.82 [0.75–0.89])

Table 3. Patient Characteristics and Risk of Major Bleeding According to Initial Dabigatran Dosage

Characteristics	Dabigatran 110 mg BID (n=6234)	Dabigatran 150 mg BID (n=9179)
Males, n (%)	2793 (44.8)	5947 (64.8)
Age, y		
Mean (SD)	80.1 (8.1)	65.6 (8.6)
Median (IQR)	81 [76, 85]	67 [61, 72]
CHA2DS2-VASc score, mean (SD)	3.7 (1.4)	2.1 (1.4)
CHA2DS2-VASc score, median [IQR]	4 [3, 5]	2 [1, 3]
CHA2DS2-VASc score (%)		
Low (score 0)	47 (0.8)	1115 (12.1)
Intermediate (score 1)	237 (3.8)	2214 (24.1)
High (score >1)	5950 (95.4)	5850 (63.7)
HAS-BLED score, mean (SD)	2.48 (1.06)	1.76 (1.15)
HAS-BLED score, median [IQR]	2 [2, 3]	2 [1, 3]
HAS-BLED score (%)		
Low (score 0–1)	1181 (18.9)	3934 (42.9)
Intermediate (score 2)	1982 (31.8)	2881 (31.4)
High (score >2)	3071 (49.3)	2364 (25.8)
Major bleeding*		
30-day major bleeding	1.62 [1.11–2.38]	1.53 [0.99–2.36]
Total follow-up	1.29 [1.09–1.52]	0.98 [0.81–1.20]
30-day major bleeding (age <80 years)	0.89 [0.46–1.70]	1.26 [0.75–2.10]
Total follow-up (age <80 years)	1.07 [0.82–1.38]	0.92 [0.73–1.17]
Nonpersistence*		
Nonpersistence	1.23 [1.12–1.36]	1.65 [1.50–1.80]

BID indicates twice-daily; IQR, interquartile range.
*Presented as adjusted hazard ratio (apixaban is reference).

and rivaroxaban (HR, 0.88 [0.81–0.95]) had lower risk of nonpersistence whereas dabigatran had a higher risk (HR, 1.19 [1.14–1.24]). Sex-stratified analyses are in Table 7. In the landmark analyses of nonpersistence, dabigatran (HR, 1.57 [1.34–1.85]) had an increased risk, warfarin (HR, 0.31 [0.26–0.37]) a decreased risk, and rivaroxaban a similar risk (HR, 1.01 [0.81–1.26]) compared with apixaban during the first 90 days of follow-up. After the first 90 days of follow-up, the risk of nonpersistence was increased for all OACs compared with apixaban, that is, dabigatran (HR, 1.56 [1.41–1.74]), rivaroxaban (HR, 1.20 [1.05–1.36]), and warfarin (HR, 1.76 [1.59–1.95]).

Supplementary Analyses

Compared with apixaban, we found similar 30-day and total major bleeding risk for dabigatran 150 mg BID, but higher major bleeding risk for dabigatran 110 mg BID (Table 3). There were no differences in major bleeding risk with dabigatran 150 mg or dabigatran 110 mg BID compared to apixaban in patients aged <80 years. Findings (major bleeding and nonpersistence) were similar to those in the main analyses when restricted to the period with availability of all NOACs and for OAC switch and nonswitch patients (Table 8).

Discussion

This study reports contemporary data on OAC use and safety in real-life nonvalvular AF patients following the marketing of NOACs apixaban, dabigatran, and rivaroxaban. We had 3 main findings. First, apixaban and rivaroxaban initiators had a different clinical profile from dabigatran and warfarin initiators, because they were older and less often male, with higher CHA_2DS_2-VASc and HAS-BLED scores. Second, apixaban had lower 30-day and total major bleeding risk compared with rivaroxaban, dabigatran, and warfarin. Third, dabigatran and warfarin users were at higher risk of nonpersistence compared to apixaban users, whereas rivaroxaban users had similar risk.

The 3 major trials, comparing NOACs with warfarin—ARISTOTLE (apixaban), RE-LY (dabigatran), and ROCKET-AF (rivaroxaban)—have resulted in grade 1 recommendations by American and European cardiac societies.[5,6] American guidelines recommend NOAC in patients with AF with at least 2 stroke risk factors whereas European Society of Cardiology guidelines support NOAC use with 1 or more risk factors (excluding female sex without other stroke risk factors). Indirect comparisons of trial data showed no noteworthy difference in efficacy between NOACs, but a potentially lower risk of major bleeding for apixaban.[15,16]

Overall, the rate of major bleeding events ranged from 2.9 to 4.3 per 100 person-years in our study. These are higher than those reported in trial data (2.1–3.6%/year) and are readily explained by inclusion of older and unselected patients in this real-world setting. In addition, definitions of bleeding were not identical, given that our study included only serious bleeding requiring hospitalization whereas trial events were adjudicated from clinical workup. Given that new agents are approved beyond a controlled setting, the addition of real-world complications should be appreciated because the degree of clinically meaningful events from trials have been recognized as a major limitation.[17] Dabigatran had the lowest major bleeding rate, whereas apixaban had a lower adjusted risk of major bleeding (both total and within 30 days of initiation) than rivaroxaban, dabigatran, and warfarin. A recent

Table 4. Number and Percentage of First-Time Switchers

Initiation OAC Group	Switch to (Row %)				
	Apixaban	Rivaroxaban	Dabigatran	Warfarin	Total No. of Switchers (% of Total Initiated)
Apixaban (n=7963)	—	93 (22)	63 (15)	270 (63)	426 (5)
Rivaroxaban (n=6715)	182 (27)	—	198 (29)	305 (45)	685 (10)
Dabigatran (n=15 413)	550 (20)	703 (26)	—	1495 (54)	2748 (19)
Warfarin (n=24 230)	564 (20)	758 (28)	1430 (52)	—	2752 (11)

OAC indicates oral anticoagulant.

post-hoc analysis of ROCKET-AF showed that rivaroxaban users had significantly higher risk of major and nonmajor gastrointestinal bleeding compared with warfarin users (HR, 1.42), which support potential differences found between apixaban and rivaroxaban in the present study.[18] A study of elderly Medicare beneficiaries found that dabigatran users had increased gastrointestinal bleeding compared to warfarin users, although overall major bleeding risk was similar.[19] In contrast to the clinical trials, we found the increased major bleeding risk most pronounced for females taking dabigatran and warfarin compared to apixaban. There was no difference by sex in bleeding risk in the ARISTOTLE (apixaban) and ROCKET-AF (rivaroxaban) trials; RE-LY did not report these data. Although not supported by the pivotal trials, a meta-analysis including 7 trials of NOACs concluded that women have a higher bleeding risk than men in acute venous thromboembolism treated by NOAC.[20] Possible mechanisms include differences in creatinine clearance, volume distribution, and drug uptake between men and women.[21] Our finding suggests a need for future investigations (preferably randomized) of sex-related differences in bleeding between OAC drugs.

When separating dabigatran into 110 and 150 mg BID, we confirmed previous registry-based findings that lower-dose dabigatran was associated with higher major bleeding risk when compared to warfarin.[22,23] This is in contrast to RE-LY and partly in contrast to results from a Medicare claims analysis.[19] The latter study consisted of an elderly AF population (aged >65 years) using the nontrial dosage of dabigatran 75 mg BID and reported only gastrointestinal (nonsignificant increase in bleeding with high-dose dabigatran) and intracranial bleeding (nonsignificant increase in

Table 5. Risk of Major Bleeding and Nonpersistence

		Apixaban		Rivaroxaban		Dabigatran		Warfarin	
Availability of follow-up, days									
Mean (SD)		268.4 (220.1)		348.5 (324.1)		511.4 (438.0)		398.0 (374.6)	
Median (IQR)		214 (85–397)		230 (89–549)		392 (119–821)		251 (129–564)	
	Population (Total No. of Events)	No. Events	HR [95% CI]	No. Events	HR [95% CI]	No. Events	HR [95% CI]	No. Events	HR [95% CI]
Major bleeding									
Total major bleeding	54 321 (2418)	252	Reference	343	1.49 [1.27–1.77]	695	1.17 [1.00–1.38]	1128	1.23 [1.05–1.43]
30-day major bleeding	54 321 (448)	52	Reference	71	1.69 [1.18–2.43]	123	1.64 [1.15–2.34]	202	1.41 [1.01–1.96]
Nonpersistence									
Risk of 30-day gap in treatment	54 321 (14 800)	688	Reference	605	1.07 [0.96–1.20]	3418	1.45 [1.33–1.59]	10 089	1.22 [1.12–1.33]

HR indicates hazard ratio; IQR, interquartile range.

Table 6. Distribution and Type of Major Bleeding

Type of Major Bleeding	No. (%)
Intracranial	399 (17)
Gastrointestinal	1022 (42)
Respiratory	276 (11)
Pericardial	16 (1)
Ocular	19 (1)
Renal/urinary	454 (19)
Anemia	232 (10)
Total	2418 (100)

bleeding with low-dose dabigatran). Our finding may be influenced by unmeasured confounders or selection bias: For example, dabigatran 110 mg BID users were, on average, >14 years older and had higher HAS-BLED (2.5 vs 1.8) than dabigatran 150 mg BID users. When restricting the analyses to patients aged <80 years (ie, excluding patients where only low dosage is recommended), we found no differences in major bleeding risk using apixaban as reference. Thus, prescribing physicians may systematically select patient for lower dosages because of perceived (and possibly correctly) increased bleeding risk, which is reflected in the observed higher bleeding rates in the dabigatran 110 mg group. Studies investigating potential physician preferences and prescription patterns according to dosages are most welcome. In the clinical trials, discontinuation risk was lower for apixaban (2310 of 9088 [25.4%] vs 2493 of 9052 [27.5%] patients), but higher for rivaroxaban (23.7% vs 22.2%) and dabigatran (14.5–15.5% vs 10.2%) compared with warfarin. In our study, the cumulative incidence curve of nonpersistence (Figure 4) showed better persistence to the NOACs than to warfarin. Although definitions of persistence between the trials and the present study are not readily comparable, it is reassuring that these new agents seem to yield persistence in 70% to 85% of patients after 3 years; this is considerably higher than the 40% observed for warfarin. However, it should be recognized that the method used is based on prescription claims. Following the initiation of treatment, some treatment episodes last longer (warfarin and rivaroxaban), attributed to differences in pack sizes, and this likely affect the results. Notably, findings from our landmark analyses suggest that warfarin users initially had very good persistence, but when looking beyond the first 90 days, we found, from the cumulative incidence and the adjusted Cox model, higher persistence for apixaban and rivaroxaban and lower for dabigatran and warfarin. The fact that gastrointestinal side effects have frequently been reported in dabigatran users could potentially be a mechanism behind our finding that dabigatran users were more likely to be nonpersistent

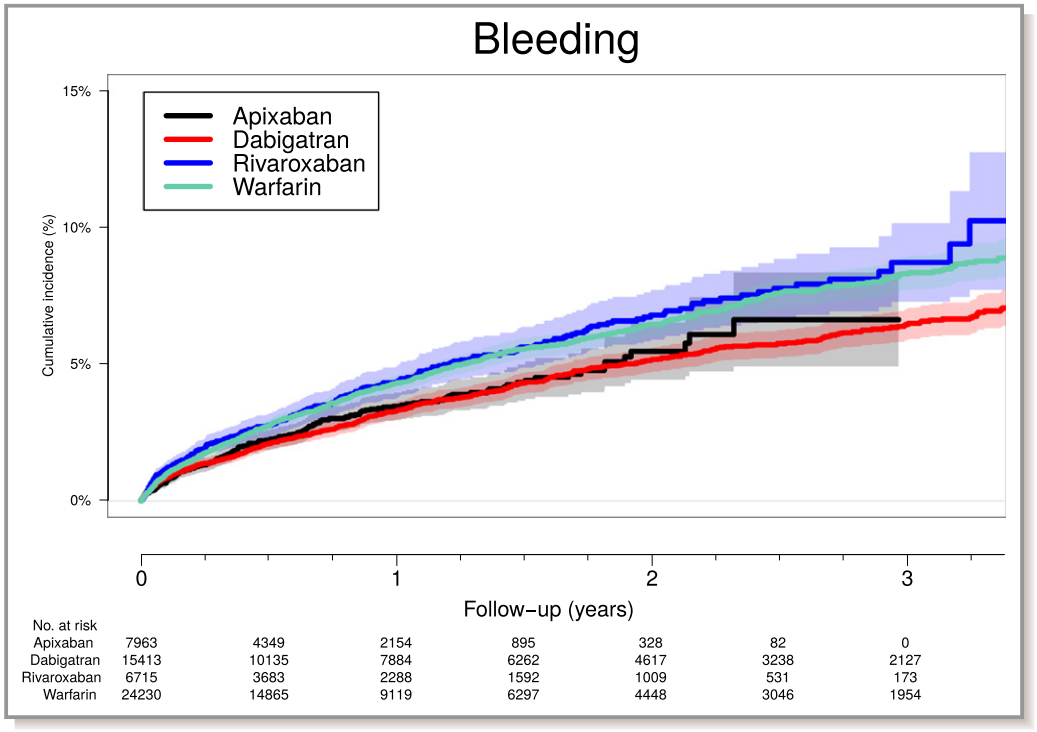

Figure 3. Cumulative incidence of major bleeding according to OAC treatment. Cumulative incidence of major bleeding according to OAC treatment (nonswitch patients only) taking into account competing of death. OAC indicates oral anticoagulant.

Table 7. Sex-Stratified Analyses of Risk of Major Bleeding and Nonpersistence

	Population (Total No. of Events)	Apixaban		Rivaroxaban		Dabigatran		Warfarin	
		No. Events	HR [95% CI]	No. Events	HR [95% CI]	No. Events	HR [95% CI]	No. Events	HR [95% CI]
Major bleeding									
Total major bleeding (Female)	23 883 (966)	102	Reference	133	1.47 [1.12–1.91]	308	1.45 [1.13–1.85]	423	1.46 [1.14–1.86]
Total major bleeding (Male)	30 438 (1452)	150	Reference	210	1.51 [1.22–1.88]	387	1.01 [0.82–1.24]	705	1.08 [0.89–1.32]
30-day major bleeding (Female)	23 883 (182)	18	Reference	32	2.31 [1.29–4.15]	49	2.15 [1.20–3.86]	83	2.06 [1.19–3.57]
30-day major bleeding (Male)	30 438 (266)	34	Reference	39	1.35 [0.85–2.16]	74	1.36 [0.87–2.14]	119	1.08 [0.71–1.64]
Nonpersistence									
Risk of 30 day gap in treatment (female)	23 883 (6226)	260	Reference	235	1.10 [0.92–1.32]	1307	1.64 [1.43–1.89]	4424	1.66 [1.45–1.90]
Risk of 30-day gap in treatment (male)	30 438 (8574)	428	Reference	370	1.05 [0.91–1.20]	2111	1.32 [1.18–1.47]	5665	0.97 [0.88–1.08]

HR indicates hazard ratio.

compared with apixaban users.[19,24] Several compliance studies have shown that persistence to treatment is strongly affected by the number of tablets taken daily.[25] Perhaps surprisingly, our data suggested that rivaroxaban (given OD) users did not have lower risk of nonpersistence compared with apixaban users (given BID). Periods off treatment are very

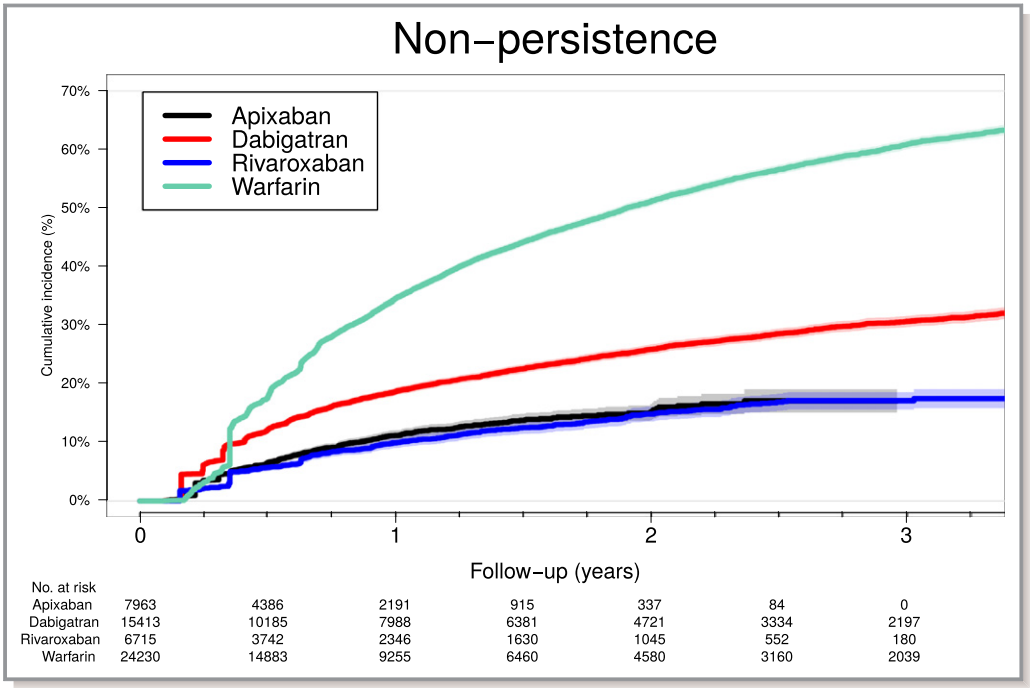

Figure 4. Cumulative incidence of nonpersistence according to OAC treatment. Cumulative incidence of nonpersistence (defined as more than a 30-day gap in treatment) according to OAC treatment (nonswitch patients only) taking into account competing of death. OAC indicates oral anticoagulant.

Table 8. Risk of Major Bleeding and Nonpersistence Following Full NOAC Availability and According to Switch Status

	Population (Total No. of Events)	Apixaban		Rivaroxaban		Dabigatran		Warfarin	
		No. Events	HR [95% CI]	No. Events	HR [95% CI]	No. Events	HR [95% CI]	No. Events	HR [95% CI]
Major bleeding*									
Total major bleeding (debut apixaban)	36 762 (1427)	244	Reference	283	1.48 [1.24–1.76]	337	1.15 [0.96–1.37]	563	1.23 [1.04–1.45]
30-day major bleeding (debut apixaban)	36 762 (312)	52	Reference	65	1.66 [1.15–2.40]	70	1.53 [1.04–2.24]	125	1.45 [1.03–2.04]
Total major bleeding (OAC nonswitch)	54 321 (2180)	221	Reference	280	1.49 [1.25–1.79]	612	1.13 [0.95–1.34]	1067	1.21 [1.02–1.42]
30-day major bleeding (OAC nonswitch)	54 321 (440)	51	Reference	70	1.73 [1.20–2.49]	118	1.62 [1.13–2.32]	201	1.42 [1.02–1.99]
Total major bleeding (OAC switch)	6611 (238)	31	Reference	63	1.51 [0.98–2.34]	83	1.47 [0.95–2.29]	61	1.25 [0.80–1.97]
Nonpersistence									
Risk of 30-day gap in treatment (debut apixaban)	36 762 (6921)	683	Reference	505	1.02 [0.91–1.15]	1756	1.50 [1.37–1.65]	3977	1.20 [1.10–1.30]
Risk of 30-day gap in treatment (OAC nonswitch)	54 321 (14 597)	664	Reference	579	1.07 [0.96–1.20]	3371	1.45 [1.32–1.58]	9983	1.22 [1.12–1.33]
Risk of 30-day gap in treatment (OAC switch)	1001 (203)	24	Reference	26	1.01 [0.58–1.77]	47	1.97 [1.16–3.33]	106	1.13 [0.71–1.80]

HR indicates hazard ratio; NOAC, nonvitamin K antagonist oral anticoagulant; OAC, oral anticoagulant.
*Too few events to assess 30-day major bleeding risk in OAC switch patients.

worrisome given short half-life elimination (range, 10–17 hours) and may place patients at markedly increased thromboembolic risk.[26] The degree of suboptimal protection needs to be investigated further as well as any markers of interruption of treatment.

Do these data aid in the selection of OAC for the practicing clinician and patients? We found highest persistence to apixaban and rivaroxaban, fewer major bleeding complications with apixaban overall, and some evidence that women taking dabigatran and warfarin may be at further increased risk of major bleeding compared to men. Even though causality is a challenge in observational data, these findings warrant attention. Our findings suggest that, in a real-life clinical setting, uptake and safety issues differ between NOACs. Clarification for health care providers and patients will require future observational studies with information on prescription patterns (including sex differences) and assessment of effectiveness, given that randomization between NOACs seems unimaginable at the moment.

Limitations

Despite providing updated and real-life data on experience from OAC use, our study is limited by its observational nature. The Danish population consists of a racially homogeneous population of mainly whites, which makes extrapolation of the results to other populations limited. Although indications of use should be similar across the different OAC cohorts in our study, the potential for selection bias should be recognized. Concerning unmeasured confounders, we did not have information on left ventricle ejection fraction, on tobacco use, degree of potential renal dysfunction, body mass index, or patient and physician preferences. Our definition of major bleeding includes all episodes requiring hospitalization; and hospital databases have shown high precision for registration of bleeding events.[27] The diagnostic coding for AF has previously been validated with high positive predictive value (97%).[28] Also, our analyses do not take local or regional recommendations or policies of first-line OAC use into

account. We confirm data from a previous study that the proportions initiating OAC treatment change over time (dabigatran and warfarin initiation declined, whereas apixaban and rivaroxaban increased).[29] The decline of warfarin use is most likely explained by increased NOAC use, whereas the decline in dabigatran partly can be explained that elderly is less likely to be initiated.[29,30] The observation period of especially apixaban was shorter compared to the other cohorts attributed to later entrance to market. The possibility exists that treatment courses that span multiple prescriptions claims might be subject to more episodes off treatment. However, we do not believe this would strongly affect our findings given that we took the switch to another OAC into account (and also performed analyses with censoring at time of switch), performed sensitivity analyses in the period when all NOACs were available, and used methods that allowed for continuous exposure assessment. All prescriptions of OAC are captured by the databases, but our method used to define OAC exposure is an approximation. Given that actual intake of tablets is unknown (data based on prescription claims) and likely to be closely related to a recent prescription claim, this could have affected our findings. However, because there is only partial reimbursement of drug expenses in Denmark, patient copayment would indicate an intention to take the claimed prescription. Furthermore, given that analyses of shorter-term major bleeding risk (within 30 days) are consistent with results from the total follow-up period, we believe our method to be valid in assessing an association between OAC exposure and bleeding.

Conclusions

In a contemporary real-life cohort of nonvalvular AF patients, differences in major bleeding complications and persistence between OAC therapies exist. Apixaban had lower 30-day and total major bleeding risk compared to rivaroxaban, dabigatran, and warfarin. Nonpersistence was highest for dabigatran and warfarin, compared to apixaban and rivaroxaban. Given that the landscape of stroke prevention in AF is rapidly evolving, results from nonrandomized studies of potential safety issues need to come to the attention to patients and health care providers. As more real-world data on NOACs accumulate, future studies should also focus on effectiveness to help inform optimal treatment decisions.

Author Contributions

Lamberts and Gislason had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Lamberts, Staerk, Olesen, Fosbøl, Hansen, and Gislason are responsible for the design and conduct of the study, collection, management, analysis, and interpretation of the data, and preparation, review, and approval of the manuscript. The sponsors of the study, Bristol Meyers-Squibb/Pfizer (Harboe, Lefevre, Evans), contributed with the design and conduct of the study and preparation, review, and approval of the manuscript.

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Disclosures

Lamberts reports receiving speaker fees from Bristol Meyers-Squibb and Bayer. Staerk has no disclosures to report. Olesen reports receiving speaker fees from Bristol-Myers Squibb and Boehringer Ingelheim, and funding for research from the Lundbeck Foundation, Bristol-Myers Squibb, and The Capital Region of Denmark, Foundation for Health Research. Fosbøl reports receiving an independent research grant from Janssen Pharmaceutical. Hansen reports receiving speaker fees from Bristol Meyers-Squibb. Harboe is currently employed at Bristol Meyers-Squibb (Denmark). Lefevre is currently employed at Bristol Meyers-Squibb (France). Evans has formerly been employed at Bristol Meyers-Squibb (France). Gislason reports receiving speaker fees from AstraZeneca, Pfizer, and Bristol-Myers Squibb. Gislason reports research grants from Bristol-Myers Squibb and a scientific advisor position for AstraZeneca.

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