American Journal of Epidemiology

Vol. 00, No. 00
DOI: 10.1093/aje/kwaa133
Advance Access publication:

Original Contribution

Using the Case-Crossover Design to Assess Short-Term Risks of Bleeding and Arterial Thromboembolism After Switching Between Oral Anticoagulants in a Population-Based Cohort of Patients With Atrial Fibrillation

Maja Hellfritzsch*, Shirley V. Wang, Erik Lerkevang Grove, Joshua J. Gagne, Jesper Hallas, and Anton Pottegård

* Correspondence to Dr. Maja Hellfritzsch, Clinical Pharmacology and Pharmacy, University of Southern Denmark, J.B. Winsløws Vej 19, 2, DK-5000 Odense C, Denmark (email: mmhellfritzsch@health.sdu.dk).

Initially submitted August 6, 2019; accepted for publication July 2, 2020.

Using nationwide Danish registries, we conducted a population-based case-crossover study evaluating the association between switching from a vitamin K antagonist (VKA) to a direct oral anticoagulant (DOAC), and vice versa, and 30-day risks of bleeding and arterial thromboembolism in patients with atrial fibrillation (AF). The case-crossover population was identified among oral anticoagulant users during 2011–2018 (n = 123,217) as patients with AF with 1) a case-defining outcome and 2) an anticoagulant switch during the 180 days preceding the outcome. Odds ratios were estimated using conditional logistic regression by comparing the occurrence of switching during the 30-day window immediately preceding the outcome to that in reference windows in the same individual 60–180 days before the outcome. The case-crossover populations for switching from VKA to DOAC and DOAC to VKA comprised 1,382 and 287 case patients, respectively. Switching from VKA to DOAC, but not from DOAC to VKA, was associated with an increased short-term risk of bleeding (odds ratio = 1.42; 95% confidence intervals: 1.13, 1.79, and 1.06; and 0.64, 1.75, respectively) and ischemic stroke (odds ratio = 1.74; 95% confidence intervals: 1.21, 2.51, and 0.92; and 0.46, 1.83, respectively). Our findings suggest that switching from VKA to DOAC is an intermittent risk factor of bleeding and ischemic stroke in patients with AF.

anticoagulants; atrial fibrillation; confounding; pharmacoepidemiology; thromboembolism

Abbreviations: AF, atrial fibrillation; CI, confidence interval; DOAC, direct oral anticoagulant; OR, odds ratio; VKA, vitamin K antagonist.

The direct oral anticoagulants (DOACs; namely, dabigatran, rivaroxaban, apixaban, and edoxaban) have comparable efficacy to the traditional vitamin K antagonists (VKAs) when used for stroke prevention in atrial fibrillation (AF) (1). However, DOAC and VKA therapy differ in several aspects, such as monitoring, interactions with drugs and food, and adverse-effect profiles (2). Accordingly, switching between the 2 drug groups is common (3–7).

Although short interruptions in anticoagulant therapy will leave a patient with AF vulnerable to ischemic stroke (8), overlap of anticoagulant drug effects are likely to increase the risk of bleeding (9, 10). Thus, a key aspect of oral anticoagulant switching is to ensure sufficient anticoagulation coverage while minimizing the time of overlap between drugs. This balance can be difficult to achieve, however. This was illustrated after the termination of the pivotal clinical trials in which participants switching from blinded DOAC treatment to open-label VKA therapy had a markedly higher 30-day risk of bleeding and thrombosis compared with those using VKAs both during and after the trial (8, 11).

Despite the high incidence of switching in patients with AF in clinical practice, real-world evidence is lacking on the short-term risks associated with switching between oral anticoagulants relative to uninterrupted anticoagulant therapy (12). In this study, our objective was to evaluate the association between anticoagulant switching and short-term risk of bleeding, arterial thromboembolic events, and all-cause death in patients with AF switching from VKA to DOAC and from DOAC to VKA.

METHODS

Using data from nationwide Danish health registries (described in the Web Appendix 1, available at https://academic.oup.com/aje), we conducted a case-crossover study estimating the short-term relative risk of bleeding, arterial thromboembolism, and death associated with switching between oral anticoagulants in patients with AF.

Study design

Patients who switch anticoagulant treatment differ from patients who do not switch (13, 14). Accordingly, observational studies exploring risks and benefits of anticoagulant switching are prone to confounding from unequal distribution of characteristics potentially related to the risk of outcomes during anticoagulant therapy, such as the ability to achieve a sufficient "time in therapeutic range" of the international normalized ratio on VKA therapy (12, 15, 16). In acknowledgement hereof, we used a self-controlled design: a case-only design with the ability to control, by design, between-person confounding as well as within-person time-stable confounding (17). Because we aimed to study the association between a transient exposure (i.e., switching) and an abrupt onset clinical outcome, we applied the case-crossover design (Web Figure 1) (18). The basic methodology of this design is a "within-subject" comparison of exposure status (exposed or nonexposed) in the time window leading up to an outcome to exposure status during reference time windows in the past (19) (i.e., a comparison of the observed with the expected frequency of exposure within an individual).

Study cohort and case-crossover population

The study cohort from which case patients were identified consisted of all Danish residents aged 18 years or older receiving oral anticoagulant therapy (i.e., VKA or DOAC) for AF during the period August 2011 through December 2018. In Denmark, warfarin accounts for greater than 95% of the total use of VKAs (20). Criteria for cohort inclusion, exclusion, and censoring are described in detail in the Web Appendix 1 and Figure 1. In a case-crossover analysis, individuals not experiencing an outcome and outcome cases with constant exposure status over the period of evaluation (whether exposed or unexposed) do not contribute information to the estimate of association. Accordingly, to identify the case-crossover population, we first identified case patients (i.e., cohort members with an outcome, described later in the next section). Second, case patients were restricted to those who had been exposed at some point during the period of evaluation (i.e., had switched oral anticoagulant therapy within the 6 months leading up to the outcome). Case patients with no eligible reference window due to recent cohort entry were excluded from the case-crossover population, as were case patients only exposed during the washout window; neither of these would contribute information to the analysis.

Outcomes

Outcomes included 1) bleeding events categorized into any, gastrointestinal, and intracranial bleeding; 2) arterial thromboembolic events, which were a composite of ischemic stroke, transient ischemic attack, and systemic embolism (collectively referred to as "ischemic stroke") as well as myocardial infarction; and 3) all-cause death. For each outcome (e.g., ischemic stroke), only the first occurrence of that specific type of outcome during the study period was included. Each individual could contribute more than 1 type of case-defining outcome (i.e., serve as a case for more than 1 type of outcome, such as the first as an ischemic stroke case and later as a mortality case). However, outcomes contributed by the same individual were required to be separated by a minimum of 180 days to ensure they were discrete events and thereby avoid bias introduced by correlated events.

Exposure

A switch between oral anticoagulants was defined as the filling of another type of oral anticoagulant (i.e., VKA or DOAC) than the 1 most recently filled during the period estimated to be covered by the latter prescription. Because we aimed to explore the 30-day risk of outcomes after switching, the exposure of interest was a switch during the 30-day window preceding an outcome excluding the index date (the focal window). Also, exposure was assessed during 4 reference windows evenly distributed during the preceding 6 months (Web Figure 1). We used 4 reference windows with the intent of improving statistical precision (21). The window between days 31 and 60 before the event was used as a washout window. A patient was considered exposed during a given time window if a switch occurred and unexposed if no switch occurred.

Analysis

For descriptive purposes, we estimated quarterly incidence rates of switching from VKA to DOAC and from DOAC to VKA over time within the study cohort, using the total patient follow-up in the relevant calendar quarter of VKA use and DOAC use, respectively, as the denominator.

Within the case-crossover population, we estimated odds ratios with 95% confidence intervals for associations between switching from VKA to DOAC and from DOAC to VKA, and each of the outcomes. By comparing the frequency of exposure (e.g., switching from VKA to DOAC) in focal windows with the frequency in reference windows, an odds ratio estimating the underlying incidence-rate ratio of the outcome during exposed versus unexposed person-time was calculated (19). The odds ratios were estimated using conditional logistic regression (conditional on the individual). The odds ratio can be interpreted as an estimate of the 30-day event risk after switching relative to the specific patient's "usual" 30-day event risk. Considering the inherent adjustment for measured and unmeasured time-invariant confounders by design along with the short period

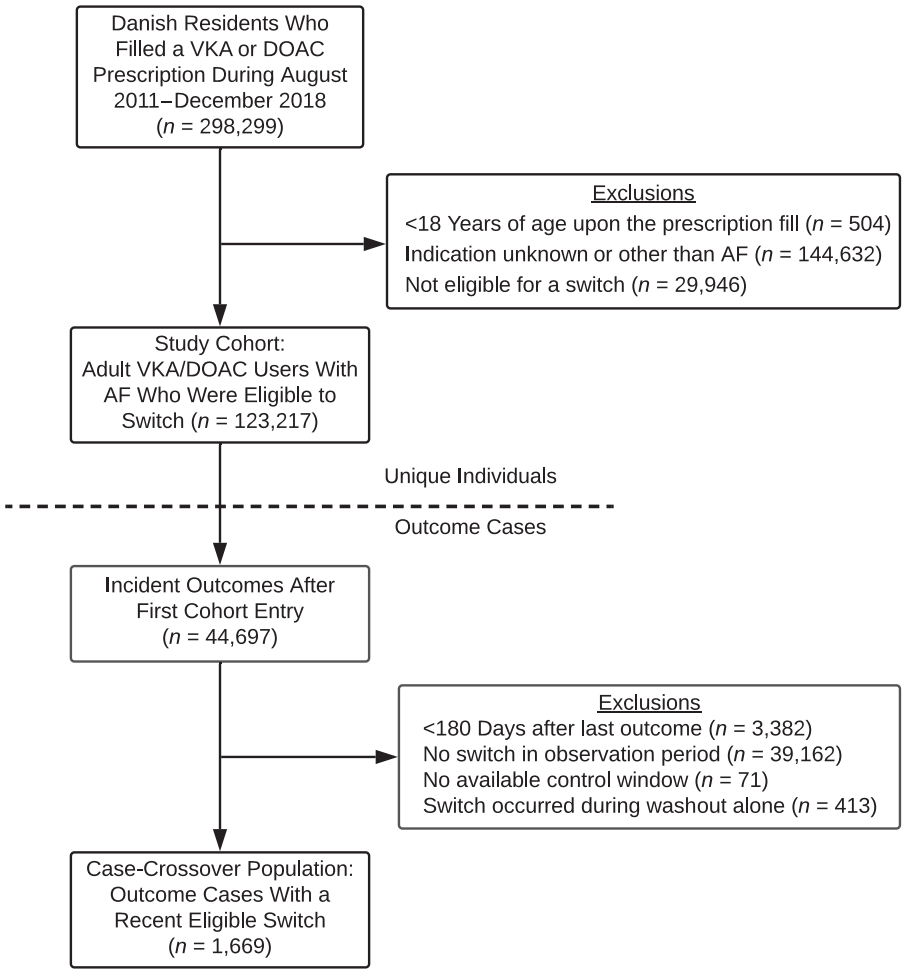

Figure 1. Flow chart describing the selection of the study cohort of patients with atrial fibrillation (AF) using direct oral anticoagulants (DOAC) or vitamin K antagonists (VKA) (patient-level numbers), and within this, the case-crossover population (event-level numbers), Denmark, 2011–2018.

of exposure assessment (maximum, 6 months), no additional confounder adjustment was performed in the main analysis.

Supplementary analyses

We conducted a number of preplanned subgroup and sensitivity analyses. The analyses are described here in brief and in detail in the Web Appendix 1. First, we stratified the analyses according to potentially effect-modifying patient characteristics. Second, we repeated the analyses with a narrower (15 days) as well as a wider (60 days) windows for exposure assessment. Third, to take potential time-varying confounding into account, we performed a subgroup analysis excluding patients with a hospitalization shortly before switching (within 10 days). Fourth, because the very first users of a drug may differ from later users (22–24), we performed a subgroup analysis restricted to DOAC users entering the study cohort from March 1, 2012, and onward. Fifth, potential time trends in the exposure were accounted for using a case-time control approach (25). This analytical approach is similar to the case-crossover method but adjusts for time trends estimated in a control population. Finally, we omitted collapsing treatment episodes with fewer than 60 days between defined discontinuation of the first episode and initiation of the next.

Other

All analyses were performed using STATA 15.0 (StataCorp, College Station, Texas). The Danish Data Protection Agency approved the study (approval no. 16/13916). In Denmark, studies based solely on register data do not require ethics committee approval (26).

RESULTS

The study cohort comprised 123,217 patients with AF who used oral anticoagulants (Figure 1) contributing 154,283 treatment episodes. Within the study cohort,

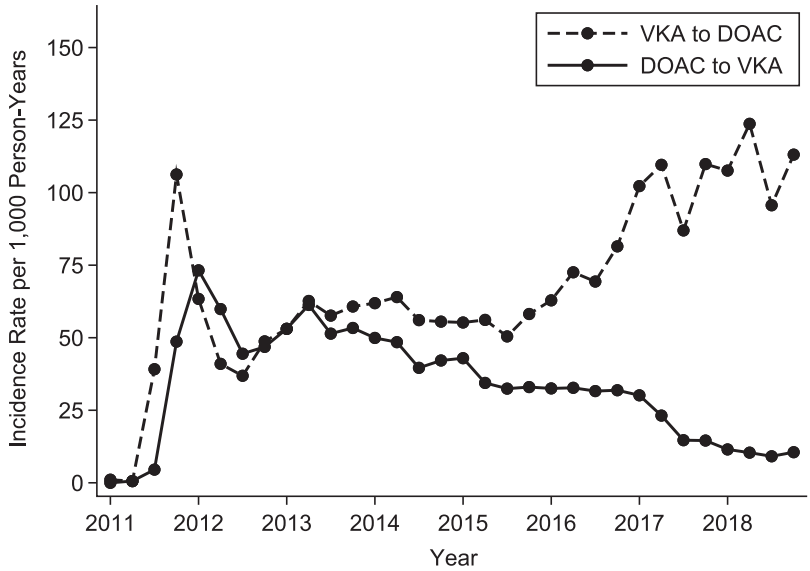

Figure 2. Incidence rates of switching from vitamin K antagonists (VKAs) to direct oral anticoagulants (DOACs) and from DOACs to VKAs among Danish patients with atrial fibrillation who use oral anticoagulants, assessed during each calendar quarter of the study period, Denmark, 2011–2018.

switching from VKA to DOAC and from DOAC to VKA was common during the first year of DOAC availability for AF (Figure 2). In the following years, both types of switching occurred at a relatively stable rate (incidence rates were approximately 60 per 1,000 person-years). During the last years of the study period, the incidence of switching from VKA to DOAC increased steadily, whereas the incidence of DOAC to VKA switching declined considerably.

Of the 44,697 incident outcomes registered within the study cohort, 2,153 (5% of all outcomes) had been preceded by a switch in oral anticoagulant therapy during the last 6 months. After exclusions (Figure 1), the case-crossover population comprised 1,669 outcome cases contributed by 1,580 unique individuals. The preceding switch had been from VKA to DOAC in 1,382 case patients (82%), and all-cause mortality was the most common case-defining outcome. Characteristics of the case-crossover population are provided in Web Table 2. Switchers from VKA to DOAC were older (median age, 83 vs. 77 years, respectively) and more often female (46% vs. 41%, respectively) than patients who switched from DOAC to VKA. Within both switch groups in the case-crossover population, the median age of case patients increased from the early to the late part of the study (from 81 to 84 years and from 75 to 82 for switchers from VKA to DOAC and from DOAC to VKA, respectively).

The distribution of exposure across the observation period is depicted for each outcome in Web Figure 2 (VKA to DOAC) and Web Figure 3 (DOAC to VKA). The frequency of exposure during focal and reference windows (i.e., the observed and the expected frequency of exposure, respectively) are reported in Web Tables 3 and 4. Corresponding odds ratios with 95% confidence intervals are provided in Table 1 and Table 2, respectively, as well as in Web Table 5 (which lists site-specific bleeding outcomes).

Switching from VKA to DOAC was associated with an increased short-term risk of any bleeding (odds ratio (OR) = 1.42, 95% confidence interval (CI): 1.13, 1.79) and gastrointestinal bleeding (OR = 1.72, 95% CI: 1.24, 2.40). The estimated risk of intracranial bleeding had low precision but appeared to be unaffected by a recent switch (OR = 0.76, 95% CI: 0.26, 2.22). The short-term risk of ischemic stroke (OR = 1.74, 95% CI: 1.21, 2.51), but not myocardial infarction (OR = 0.93, 95% CI: 0.48, 1.78), was increased after switching from VKA to DOAC.

The analyses of short-term risks after switching from DOAC to VKA had low power. Neutral associations were found for switching from DOAC to VKA and short-term risk of any bleeding and ischemic stroke (OR = 1.06, 95% CI: 0.64, 1.75; and 0.92, 95% CI: 0.46, 1.83, respectively). Switching from VKA to DOAC and from DOAC to VKA was associated with an increased short-term risk of death with odds ratios of 1.81 (95% CI: 1.56, 2.09) and 1.68 (95% CI: 1.16, 2.43), respectively.

Overall, the analyses stratified by case-patient characteristics were imprecise (Tables 1 and 2). Although this imprecision precluded identification of significant effect modifiers, some trends were observed. Age seemed to modify the associations between both types of switching and short-term risk of death, with the associations being strongest for case patients aged 80 years or older. As an example, the odds ratio for the association between switching from VKA to DOAC and 30-day risk of death was 1.91 (95% CI: 1.61, 2.26) in

Table 1. Associations, Overall and Stratified by Subgroup, Between Switching From a Vitamin K Antagonist to a Direct Oral Anticoagulant and 30-Day Risk of Case-Defining Outcomes in Patients With Atrial Fibrillation in Denmark, 2011–2018

Subgroup	Any Bleeding[a] (*n* = 367)		Ischemic Stroke/TIA/SE (*n* = 137)		Myocardial Infarction (*n* = 55)		All-Cause Death (*n* = 823)	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Overall	1.42	1.13, 1.79	1.74	1.21, 2.51	0.93	0.48, 1.78	1.81	1.56, 2.09
DOAC type								
Dabigatran	1.28	0.85, 1.95	1.75	1.00, 3.09	0.71	0.24, 2.13	1.18	0.85, 1.64
Rivaroxaban	1.55	1.10, 2.20	1.44	0.74, 2.82	1.48	0.57, 3.86	1.99	1.57, 2.52
Apixaban	1.36	0.84, 2.19	2.12	1.04, 4.28	0.29	0.04, 2.43	2.15	1.70, 2.73
Edoxaban	2.00	0.37, 10.92					1.14	0.38, 3.47
DOAC dose								
Standard	1.16	0.83, 1.61	2.47	1.45, 4.21	0.75	0.33, 1.75	1.76	1.34, 2.32
Low	1.78	1.29, 2.47	1.30	0.78, 2.17	1.34	0.47, 3.83	1.83	1.53, 2.18
Year of index date								
2011–2013	1.11	0.71, 1.76	1.24	0.60, 2.54	1.10	0.39, 3.07	1.29	0.89, 1.87
2014–2016	1.63	1.15. 2.31	1.79	1.03, 3.10	0.88	0.28, 2.72	1.93	1.55, 2.41
2017–2018	1.47	0.97, 2.21	2.30	1.19, 4.47	0.78	0.22, 2.79	1.94	1.54, 2.45
Age group, years								
<70	0.87	0.49, 1.55	2.72	1.26, 5.86	0.68	0.15, 3.09	1.33	0.67, 2.67
70–80	1.80	1.24, 2.61	1.68	0.92, 3.10	0.83	0.30, 2.33	1.59	1.14, 2.22
>80	1.44	1.02, 2.02	1.43	0.81, 2.53	1.23	0.45, 3.41	1.91	1.61, 2.26
CHA_2DS_2-VASc-score								
0–3	1.45	0.99, 2.14	1.71	0.93, 3.14	1.08	0.41, 2.82	1.91	1.41, 2.59
≥4	1.41	1.06, 1.88	1.76	1.11, 2.77	0.82	0.33, 2.01	1.78	1.51, 2.11
HAS-BLED score								
0–3	1.39	1.07, 1.81	2.09	1.37, 3.18	1.07	0.53, 2.14	1.88	1.57, 2.25
≥4	1.53	0.95, 2.45	1.05	0.49, 2.23	0.40	0.05, 3.12	1.67	1.30, 2.16
Bleeding history								
No	1.59	1.25, 2.03	2.15	1.44, 3.23	1.14	0.58, 2.24	1.76	1.49, 2.08
Yes	0.67	0.32, 1.37	0.76	0.31, 1.88			1.98	1.46, 2.67
Prior ischemic stroke								
No	1.46	1.15, 1.87	1.81	1.22, 2.68	0.90	0.46, 1.78	1.74	1.48, 2.05
Yes	1.17	0.59, 2.33	1.43	0.56, 3.66			2.19	1.54, 3.13
Ischemic heart disease								
No	1.36	1.05, 1.77	1.27	0.80, 2.03	1.02	0.48, 2.18	1.90	1.62, 2.24
Yes	1.67	1.03, 2.70	3.20	1.73, 5.93	0.73	0.20, 2.61	1.44	1.02, 2.05
Diabetes								
No	1.45	1.12, 1.87	1.93	1.29, 2.90	0.75	0.34, 1.64	1.80	1.52, 2.13
Yes	1.32	0.77, 2.27	1.14	0.48, 2.69	1.72	0.51, 5.78	1.83	1.36, 2.48
Antiplatelet therapy								
No	1.42	1.13, 1.80	1.80	1.24, 2.60	0.89	0.45, 1.75	1.82	1.57, 2.11
Yes	1.98	0.99, 3.97	1.76	0.57, 5.42	0.43	0.05, 3.78	1.66	1.00, 2.76

Abbreviations: CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65–74 years, sex category; CI, confidence interval; DOAC, direct oral anticoagulant; HAS-BLED, hypertension, abnormal liver/renal function, stroke history, bleeding history or predisposition, labile international normalized ratio, elderly, drug/alcohol use; OR, odds ratio; SE, systemic embolism; TIA, transient ischemic attack; VKA, vitamin K antagonist.

[a] The top 3 most common, site-specific bleeding types included gastrointestinal bleeding, epistaxis, and hematuria, accounting for 32%, 21%, and 17% of cases, respectively.

Table 2. Associations, Overall and Stratified by Subgroup, Between Switching From a Direct Oral Anticoagulant to a Vitamin K Antagonist and 30-Day Risk of Case-Defining Outcomes in Patients with Atrial Fibrillation in Denmark, 2011–2018

Subgroup	Any Bleeding[a] (*n* = 84)		Ischemic Stroke/TIA/SE (*n* = 49)		Myocardial Infarction (*n* = 21)		All-Cause Death (*n* = 133)	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Overall	1.06	0.64, 1.75	0.92	0.46, 1.83	1.25	0.48, 3.28	1.68	1.16, 2.43
DOAC type[b]								
Dabigatran	0.72	0.31, 1.65	0.79	0.29, 2.12	1.27	0.39, 4.12	1.78	1.01, 3.15
Rivaroxaban	1.28	0.48, 3.39	1.98	0.66, 5.95	2.17	0.35, 13.47	1.51	0.77, 2.94
Apixaban	1.48	0.63, 3.45	0.28	0.03, 2.38			1.88	0.92, 3.84
DOAC dose								
Standard	1.02	0.54, 1.93	0.60	0.23, 1.61	1.65	0.47, 5.84	0.85	0.39, 1.84
Low	1.12	0.49, 2.55	1.58	0.59, 4.23	0.87	0.18, 4.12	2.20	1.43, 3.39
Year of index date								
2011–2013	0.68	0.23, 2.08	2.09	0.67, 6.52	1.25	0.22, 7.14	2.61	1.19, 5.76
2014–2016	0.91	0.43, 1.92	0.45	0.15, 1.33	1.46	0.39, 5.51	1.55	0.95, 2.54
2017–2018	1.91	0.79, 4.62	1.90	0.35, 10.41			1.36	0.60, 3.08
Age group, years								
<70	0.76	0.34, 1.71	0.93	0.29, 2.99			1.19	0.48, 3.00
70–80	1.16	0.51, 2.60	0.65	0.19, 2.20	1.39	0.42, 4.61	0.93	0.37, 2.30
>80	1.81	0.61, 5.34	1.41	0.41, 4.91			2.23	1.41, 3.53
CHA_2DS_2-VASc-score								
0–3	1.18	0.59, 2.33	0.46	0.16, 1.34	1.16	0.23, 5.83	1.52	0.67, 3.47
≥4	0.94	0.44, 1.98	2.01	0.78, 5.20	1.30	0.39, 4.36	1.73	1.14, 2.61
HAS-BLED score								
0–3	0.84	0.46, 1.53	0.67	0.29, 1.54	1.74	0.63, 4.79	1.99	1.20, 3.29
≥4	2.11	0.81, 5.51	2.41	0.67, 8.66			1.39	0.80, 2.41
Bleeding history								
No	0.92	0.51, 1.66	1.04	0.50, 2.17	1.61	0.59, 4.36	1.55	1.00, 2.40
Yes	1.65	0.61, 4.45	0.43	0.05, 3.50			2.09	1.05, 4.16
Prior ischemic stroke								
No	0.92	0.54, 1.58	0.80	0.38, 1.69	1.08	0.38, 3.07	1.97	1.32, 2.95
Yes	5.67	0.95, 34.04					0.80	0.30, 2.14
Ischemic heart disease								
No	1.34	0.77, 2.35	0.89	0.40, 1.97	2.09	0.67, 6.47	1.84	1.20, 2.82
Yes	0.46	0.13, 1.57	1.02	0.27, 3.85	0.39	0.05, 3.29	1.32	0.63, 2.75
Diabetes								
No	1.37	0.79, 2.37	1.00	0.49, 2.06	1.54	0.57, 4.19	1.79	1.13, 2.82
Yes	0.34	0.08, 1.48	0.48	0.05, 4.39			1.51	0.80, 2.83
Antiplatelet therapy								
No	1.06	0.64, 1.78	0.97	0.49, 1.93	1.33	0.50, 3.52	1.73	1.19, 2.52
Yes	1.07	0.33, 3.53	1.81	0.33, 9.93			1.94	0.75, 5.03

Abbreviations: CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65–74 years, sex category; CI, confidence interval; DOAC, direct oral anticoagulant; HAS-BLED, hypertension, abnormal liver/renal function, stroke history, bleeding history or predisposition, labile international normalized ratio, elderly, drug/alcohol use; OR, odds ratio; SE, systemic embolism; TIA, transient ischemic attack; VKA, vitamin K antagonist.

[a] The top 3 most common, site-specific bleeding types included gastrointestinal bleeding, epistaxis, and hematuria, accounting for 29%, 27%, and 18% of cases, respectively.

[b] Edoxaban is not included because of very low numbers.

case patients older than 80 years and 1.33 (95% CI: 0.67, 2.67) in case patients younger than 70 years. The results indicated that the association between switching from VKA to DOAC and short-term risk of ischemic stroke became stronger over calendar time; in the latest part of the study period (2017–2018), the odds ratio was 2.30 (95% CI: 1.19, 4.47). Similarly, the association between switching from DOAC to VKA and bleeding was higher during the late than during the early years of the study ($OR_{2017–2018}$ = 1.91, 95% CI: 0.79, 4.62; vs. $OR_{2011–2013}$ = 0.68, 95% CI: 0.23, 2.08).

Some associations were affected when using alternative definitions of the risk window (Table 3 and Web Table 5). For all bleeding outcomes after switching from VKA to DOAC, odds ratios increased when changing the 30-day window to a 15-day window, as did the odds ratio for ischemic stroke. Conversely, odds ratios for death were lowest in the analyses using a 15-day focal window: 1.31 (95% CI: 1.08, 1.59) for switching from VKA to DOAC and 1.26 (95% CI: 0.76, 2.08) for switching from DOAC to VKA, and highest when using a 60-day window (OR = 2.07, 95% CI: 1.83, 2.33; and OR = 1.82, 95% CI: 1.34, 2.47, respectively).

Compared with the main analysis, the subgroup analysis restricted to case patients with at least 2 consecutive prescriptions of the initial oral anticoagulant produced higher point estimates for almost all outcomes (Table 3). In contrast, the exclusion of case patients who had been hospitalized shortly before switching led to slight attenuation of all associations between switching and arterial thromboembolic outcomes and death. In the case-time-control analysis, the control-crossover estimates varied, with odds ratios ranging from 1.01 to 1.11 (Web Table 6). Accordingly, the case-time-control estimates for both types of switching were similar to or slightly lower than the case-crossover estimates.

In a post hoc sensitivity analysis, we adjusted for potential time-varying confounding by proton-pump inhibitor and nonsteroidal anti-inflammatory drugs use as well as variables in the CHA_2DS_2-VASc (congestive heart failure, hypertension, age $\geq$75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65–74 years, sex category) and HAS-BLED (hypertension, abnormal liver/renal function, stroke history, bleeding history or predisposition, labile international normalized ratio, elderly, drug/alcohol use) scores assessed during the observation period. The analysis, in which we assumed these variables were not on the causal pathway between switching and outcomes, yielded comparable, although slightly attenuated, risk estimates compared with the main analysis (Table 3).

DISCUSSION

This population-based case-crossover study of patients with AF provide real-world data on potential short-term fluctuations in the risk of bleeding, arterial thromboembolism, and death associated with switching between oral anticoagulants. Our study indicates that switching from VKA to DOAC is associated with an increased short-term risk of bleeding and ischemic stroke, as compared with periods of stable oral anticoagulant use. Similar increased risks were not found in the analysis of switching from DOAC to VKA, which, however, had low power. Both types of switching were associated with an increased short-term risk of death. However, as indicated when stratifying by age and varying the lengths of the risk windows, switching because of increasing morbidity may have confounded these analyses.

This study has several strengths. Most importantly, the study design reduced the risk of measured and unmeasured confounding from differences in characteristics, including international normalized ratio control and genetics, between switchers and nonswitchers. Furthermore, the study was based on nationwide data sources with complete coverage and follow-up of the entire Danish population, minimizing the risk of selection bias (27).

Some limitations must be addressed. First, the case-crossover design is vulnerable to time-varying confounding (17). In the context of the present study, this type of confounding could be introduced by within-person variation in characteristics that affect both the event risk and the timing of switching during the observation period. Importantly, ischemic strokes, myocardial infarctions, and bleeding could not occur during the observation period, because of the design of the study. Also, the sensitivity analyses adjusting for potential time-varying confounding did not indicate that this was an important source of bias in our analysis. Nevertheless, as we will discuss, we do consider it likely that time-varying confounding from declining functional status may have influenced some of the results. Second, time trends in the exposure of interest may have biased the results of the case-crossover analysis (18). However, results were consistent when adjusting for time trends in the case-time-control analysis and when excluding the first large "switching wave" observed shortly after the introduction of dabigatran for AF. Third, when we used a stricter exposure definition, most associations became stronger. Thus, exposure misclassification may have led to systematic underestimation of the associations in the main analysis. Finally, although we included all relevant case patients in Denmark, the case-crossover population was relatively small. Although this was not a source of bias, but rather a result in itself, the population size did lead to low precision in most analyses. Consequently, no conclusions regarding differences between the individual DOAC drugs could be drawn.

Our finding of an increased risk of bleeding events in the early period after switching from VKA to DOAC is consistent with findings from both the Rivaroxaban Once-Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) Trial and the Dresden DOAC Registry (28, 29). Importantly, the risk of intracranial bleeding was not increased in the short-term in the present study. We also observed a nearly 2-fold increased ischemic stroke risk after switching from VKA to DOAC. The association became more pronounced when narrowing the risk window to 15 days and when optimizing the exposure definition—both supportive of a direct effect of switching. The increased risk of bleeding could reflect the slower offset of warfarin than onset of DOAC resulting in an overlap of anticoagulant effects during switching (2). In

Table 3. Supplementary Analyses of Associations Between Oral Anticoagulant Switching and 30-Day Risk of Case-Defining Outcomes in Patients With Atrial Fibrillation in Denmark, 2011–2018

Analysis	Switching From VKA to DOAC								Switching From DOAC to VKA							
	Bleeding Events (*n* = 367)		Ischemic Stroke/TIA/SE (*n* = 137)		Myocardial Infarction (*n* = 55)		All-Cause Death (*n* = 823)		Bleeding Events (*n* = 84)		Ischemic Stroke/TIA/SE (*n* = 49)		Myocardial Infarction (*n* = 21)		All-Cause Death (*n* = 133)	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Overall	1.42	1.13, 1.79	1.74	1.21, 2.51	0.93	0.48, 1.78	1.81	1.56, 2.09	1.06	0.64, 1.75	0.92	0.46, 1.83	1.25	0.48, 3.28	1.68	1.16, 2.43
Risk window, days																
15	1.95	1.45, 2.62	1.95	1.24, 3.05	0.99	0.43, 2.29	1.31	1.08, 1.59	0.98	0.53, 1.83	1.13	0.51, 2.52	1.32	0.42, 4.18	1.26	0.76, 2.08
60	1.45	1.20, 1.75	1.42	1.07, 1.88	0.96	0.59, 1.56	2.07	1.83, 2.33	1.25	0.87, 1.78	1.14	0.66, 1.98	1.29	0.56, 2.98	1.82	1.34, 2.47
Adjustment for time-variant characteristics[a]	1.29	1.02, 1.64	1.66	1.13, 2.44	0.86	0.42, 1.76	1.67	1.43, 1.95	1.05	0.61, 1.79	0.76	0.35, 1.64	0.55	0.12, 2.55	1.50	0.99, 2.27
No merging of episodes <60 days apart	1.35	1.06, 1.71	1.80	1.23, 2.63	0.85	0.43, 1.68	1.73	1.49, 2.01	1.19	0.72, 1.96	0.92	0.45, 1.89	1.42	0.53, 3.80	1.81	1.25, 2.63
Exclusion of																
<2 prescriptions on specific OAC switched from	1.58	1.23, 2.03	2.09	1.42, 3.09	1.27	0.66, 2.46	2.06	1.75, 2.42	1.36	0.72, 2.60	1.61	0.72, 3.57	1.07	0.29, 3.93	1.85	1.22, 2.80
Hospitalized ≤10 days before switch	1.44	1.10, 1.87	1.48	0.97, 2.25	0.79	0.36, 1.73	1.63	1.35, 1.96	1.29	0.74, 2.25	0.78	0.33, 1.81	1.02	0.32, 3.25	1.38	0.88, 2.19
Cohort entry later than February 2012	1.37	0.98, 1.92	1.85	1.12, 3.07	0.64	0.24, 1.72	1.75	1.42, 2.15	1.01	0.56, 1.79	1.00	0.44, 2.28	1.67	0.56, 4.94	1.21	0.72, 2.02

Abbreviations: CI, confidence interval; DOAC, direct oral anticoagulant; OAC, oral anticoagulant; OR, odds ratio; SE, systemic embolism; TIA, transient ischemic attack; VKA, vitamin K antagonist.

[a] Adjustment for changes in the use of proton pump inhibitors and nonsteroidal anti-inflammatory drugs and in the risk scores CHA2DS2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65–74 years, sex category), and HAS-BLED (hypertension, abnormal liver/renal function, stroke history, bleeding history or predisposition, labile international normalized ratio, elderly, drug/alcohol use).

contrast, the increased risk of ischemic stroke may reflect a tendency among physicians to start DOAC therapy at lower international normalized ratio levels than recommended, as has been observed in other populations (29).

Switching from DOAC to VKA after termination of the aforementioned trial as well as the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation Trial increased the 30-day risk of bleeding and arterial thromboembolism markedly (8, 11). In contrast, we found an overall neutral risk of these outcomes early after switching from DOAC to VKA. This finding could reflect an overall safe and effective switching regimen in Danish clinical practice (30), potentially due to a high quality of anticoagulant control in this setting (31). Also, low median age and prevalence of risk factors in Danish patients switching from DOAC to VKA, as previously shown (32), may have contributed to our finding of no overall increased risk of ischemic stroke and/or bleeding. As implied by prior studies, the risk of complications during transition from 1 anticoagulant to another is likely modified by the patient's susceptibility to transient changes in the anticoagulant effect, as indicated by presence of risk factors (29, 33). As such, our findings should not be interpreted as evidence of no increased risk of events after switching from DOAC to VKA in general, but rather as evidence of no increased risk in the context of current switching practice and/or in populations of switchers from DOAC to VKA similar to the Danish.

Both types of switching were associated with an increased short-term mortality risk in our analysis. Although we cannot preclude a minor increased risk of death after switching, we consider it likely that this finding, at least in part, is a product of confounding by severe frailty. According to our hypothesis, an increased mortality risk shortly after switching would primarily be explained by instability in anticoagulation causing an increased risk of potentially fatal bleeding and/or thrombotic events. However, although the association between death and switching from VKA to DOAC became stronger when expanding the risk window, the opposite pattern was found for bleeding and ischemic stroke. For switching from DOAC to VKA, the increased short-term mortality risk contrasts with the finding of no increased risk of bleeding or ischemic stroke during the same period. The observed associations between switching and short-term risk of death may be explained by case patients who switched due to accelerating morbidity such as declining renal function and perceived increased risk of bleeding and/or falling (29, 32) (i.e., factors inherently associated with a short life expectancy). This interpretation is supported by the modification of these estimates by age, because associations were strongest only in case patients older than 80 years.

Some associations became stronger over calendar time. This may be explained by a change in the risk profile of switchers over time, with more "high-risk" patients being switched toward the end of the study period. This hypothesis is supported by our finding of the observed increase in the median age of case patients over time and could reflect changes in physicians' behavior as they become increasingly familiar with a new drug group as well as changes in guidelines over time. The analyses stratified by calendar time, however, had low power, and the differences over time could simply be due to chance.

Although our study supports a biologically plausible, transiently increased risk of bleeding and ischemic stroke after switching from VKA to DOAC, we overall consider our results as reassuring. Only approximately 5% of anticoagulated patients with AF experiencing an outcome had switched anticoagulant therapy during the preceding 6 months. This finding, along with the limited strength of the observed associations, indicates that the proportions of bleeding, arterial thromboembolisms, and deaths within the population of patients with AF that could be attributed to anticoagulant switching (if the association was causal) are likely very low. Furthermore, in most anticoagulated patients with AF, the a priori 30-day risk of events is low and, therefore, a doubling of this risk represents a small absolute increment.

CONCLUSION

In patients with AF, the within-person relative risk of bleeding and ischemic stroke was slightly increased during the 30 days after switching from VKA to DOAC. Switching from VKA to DOAC should potentially be considered an intermittent risk factor of bleeding and ischemic stroke. Overall, switching from DOAC to VKA by patients with AF does not appear to be associated with short-term increases in bleeding and ischemic stroke risk in a Danish setting.

ACKNOWLEDGMENTS

Author affiliations: Clinical Pharmacology and Pharmacy, Department of Public Health, University of Southern Denmark, Odense, Denmark (Maja Hellfritzsch, Jesper Hallas, and Anton Pottegård); Department of Cardiology, Regional Hospital West Jutland, Herning, Denmark (Maja Hellfritzsch); Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts (Shirley V. Wang, Joshua J. Gagne); Harvard Medical School, Boston, Massachusetts (Shirley V. Wang, Joshua J. Gagne); Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark (Erik Lerkevang Grove); and Department of Clinical Medicine, Faculty of Health, Aarhus University, Aarhus, Denmark (Erik Lerkevang Grove).

This work was supported by The Danish Council for Independent Research (grant 95-103-21269). The funder had no influence on the conduct or the reporting of the study.

Conflict of interest: M.H. reports speaker honoraria from Bristol-Myers Squibb and Pfizer and travel grants from LEO Pharma. S.V.W. reports salary support from investigator-initiated grants to Brigham and Women's Hospital from Boehringer Ingelheim, Novartis Pharmaceuticals, and Johnson and Johnson. E.L.G. has received speaker honoraria or consultancy

fees from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Merck Sharp & Dohme, Pfizer, and Roche; and reports participation in research projects funded by AstraZeneca, with funds paid to his department (no personal fees). J.J.G. reports salary support from grants from Eli Lilly and Company and Novartis Pharmaceuticals to Brigham and Women's Hospital and consulting fees from Aetion and Optum, all for unrelated work. J.H. and A.P. report participation in research projects funded by Boehringer-Ingelheim and LEO Pharma, with funds paid to the institution where they were employed (no personal fees).

REFERENCES

1. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet*. 2014;383(9921):955–962.
2. Mega JL, Simon T. Pharmacology of antithrombotic drugs: an assessment of oral antiplatelet and anticoagulant treatments. *Lancet*. 2015;386(9990):281–291.
3. Hellfritzsch M, Husted SE, Grove EL, et al. Treatment changes among users of non-vitamin K antagonist oral anticoagulants in atrial fibrillation. *Basic Clin Pharmacol Toxicol*. 2017;120(2):187–194.
4. Tsai K, Erickson SC, Yang J, et al. Adherence, persistence, and switching patterns of dabigatran etexilate. *Am J Manag Care*. 2013;19(9):e325–e332.
5. Forslund T, Wettermark B, Hjemdahl P. Comparison of treatment persistence with different oral anticoagulants in patients with atrial fibrillation. *Eur J Clin Pharmacol*. 2016; 72(3):329–338.
6. Beyer-Westendorf J, Förster K, Ebertz F, et al. Drug persistence with rivaroxaban therapy in atrial fibrillation patients-results from the Dresden non-interventional oral anticoagulation registry. *Europace*. 2015;17(4): 530–538.
7. Kjerpeseth LJ, Ellekjaer H, Selmer R, et al. Trends in use of warfarin and direct oral anticoagulants in atrial fibrillation in Norway, 2010 to 2015. *Eur J Clin Pharmacol*. 2017;73(11): 1417–1425.
8. Patel MR, Hellkamp AS, Lokhnygina Y, et al. Outcomes of discontinuing rivaroxaban compared with warfarin in patients with nonvalvular atrial fibrillation: analysis from the ROCKET AF trial (Rivaroxaban Once-Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation). *J Am Coll Cardiol*. 2013;61(6): 651–658.
9. Douketis JD, Spyropoulos AC, Kaatz S, et al. Perioperative bridging anticoagulation in patients with atrial fibrillation. *N Engl J Med*. 2015;373(9):823–833.
10. Steinberg BA, Peterson ED, Kim S, et al. Use and outcomes associated with bridging during anticoagulation interruptions in patients with atrial fibrillation: findings from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). *Circulation*. 2015;131(5):488–494.
11. Granger CB, Lopes RD, Hanna M, et al. Clinical events after transitioning from apixaban versus warfarin to warfarin at the end of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial. *Am Heart J*. 2015;169(1):25–30.
12. Hellfritzsch M, Adelborg K, Damkier P, et al. Effectiveness and safety of direct oral anticoagulants in atrial fibrillation patients switched from vitamin K antagonists: a systematic review and meta-analysis. *Basic Clin Pharmacol Toxicol*. 2019;126(1):21–31.
13. Michalski F, Tittl L, Werth S, et al. Selection, management, and outcome of vitamin K antagonist-treated patients with atrial fibrillation not switched to novel oral anticoagulants. Results from the Dresden NOAC registry. *Thromb Haemost*. 2015;114(5):1076–1084.
14. Ikeda T, Yasaka M, Kida M, et al. A survey of reasons for continuing warfarin therapy in the era of direct oral anticoagulants in Japanese patients with atrial fibrillation: the SELECT study. *Patient Prefer Adherence*. 2018;12:135–143.
15. Suissa S, Moodie EEM, Dell'Aniello S. Prevalent new-user cohort designs for comparative drug effect studies by time-conditional propensity scores. *Pharmacoepidemiol Drug Saf.* 2017;26(4):459–468.
16. Bengtson LGS, Lutsey PL, Chen LY, et al. Comparative effectiveness of dabigatran and rivaroxaban versus warfarin for the treatment of non-valvular atrial fibrillation. *J Cardiol*. 2017;69(6):868–876.
17. Hallas J, Pottegård A. Use of self-controlled designs in pharmacoepidemiology. *J Intern Med*. 2014;275(6):581–589.
18. Gault N, Castañeda-Sanabria J, De Rycke Y, et al. Self-controlled designs in pharmacoepidemiology involving electronic healthcare databases: a systematic review. *BMC Med Res Methodol*. 2017;17(1):25.
19. Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. *Am J Epidemiol*. 1991;133(2):144–153.
20. Schmidt M, Hallas J, Laursen M, et al. Data resource profile: Danish online drug use statistics (MEDSTAT). *Int J Epidemiol*. 2016;45(5):1401–1402g.
21. Mittleman MA, Maclure M, Robins JM. Control sampling strategies for case-crossover studies: an assessment of relative efficiency. *Am J Epidemiol*. 1995;142(1):91–98.
22. Gagne JJ, Bykov K, Willke RJ, et al. Treatment dynamics of newly marketed drugs and implications for comparative effectiveness research. *Value Health*. 2013;16(6):1054–1062.
23. Wang SV, Schneeweiss S, Maclure M, et al. "First-wave" bias when conducting active safety monitoring of newly marketed medications with outcome-indexed self-controlled designs. *Am J Epidemiol*. 2014;180(6):636–644.
24. Pottegård A, Grove EL, Hellfritzsch M. Use of direct oral anticoagulants in the first year after market entry of edoxaban: a Danish nationwide drug utilization study. *Pharmacoepidemiol Drug Saf*. 2018;27(2):174–181.
25. Suissa S. The case-time-control design. *Epidemiology*. 1995; 6(3):248–253.
26. Thygesen LC, Daasnes C, Thaulow I, et al. Introduction to Danish (nationwide) registers on health and social issues: structure, access, legislation, and archiving. *Scand J Public Health*. 2011;39(7 Suppl):12–16.
27. Schmidt M, Pedersen L, Sørensen HT. The Danish civil registration system as a tool in epidemiology. *Eur J Epidemiol*. 2014;29(8):541–549.
28. Mahaffey KW, Wojdyla D, Hankey GJ, et al. Clinical outcomes with rivaroxaban in patients transitioned from vitamin K antagonist therapy: a subgroup analysis of a randomized trial. *Ann Intern Med*. 2013;158(12):861–868.
29. Beyer-Westendorf J, Gelbricht V, Förster K, et al. Safety of switching from vitamin K antagonists to dabigatran or rivaroxaban in daily care–results from the Dresden NOAC registry. *Br J Clin Pharmacol*. 2014;78(4):908–917.
30. Ruff CT, Giugliano RP, Braunwald E, et al. Transition of

patients from blinded study drug to open-label anticoagulation: the ENGAGE AF-TIMI 48 trial. *J Am Coll Cardiol*. 2014;64(6):576–584.
31. Wallentin L, Yusuf S, Ezekowitz MD, et al. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. *Lancet*. 2010;376(9745):975–983.
32. Hellfritzsch M, Grove EL, Husted SE, et al. Clinical events preceding switching and discontinuation of oral anticoagulant treatment in patients with atrial fibrillation. *Europace*. 2017; 19(7):1091–1095.
33. Mahaffey KW, Hellkamp AS, Patel MR, et al. End of study transition from study drug to open-label vitamin K antagonist therapy: the ROCKET AF experience. *Circ Cardiovasc Qual Outcomes*. 2013;6(4):470–478.