Using the Case-crossover Design to Assess Short-term Risks of Bleeding and Arterial Thromboembolism Following Switching Between Oral Anticoagulants in a Population-based Cohort of Atrial Fibrillation Patients

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Running head: Risks Associated With Anticoagulant Switching

ABSTRACT

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 atrial fibrillation (AF) patients. The case-crossover population was identified among oral anticoagulant users during 2011-2018 (n=123,217), as AF patients with (a) a case-defining outcome and (b) 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 counted 1,382 and 287 cases, 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%CI 1.13-1.79 and 1.06; 95%CI 0.64-1.75, respectively) and ischemic stroke (Odds Ratio 1.74; 95%CI 1.21-2.51 and 0.92; 95%CI 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 AF patients.

Keywords: pharmacoepidemiology; confounding; anticoagulants; atrial fibrillation; thromboembolism

Abbreviations: AF, Atrial Fibrillation; CI, Confidence Interval; DOAC; Direct Oral Anticoagulant; OR, Odds Ratio; VKA, Vitamin K Antagonist

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

While 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, however, be difficult to achieve. This was illustrated after the termination of the pivotal clinical trials in which participants switching from blinded DOAC to open-label VKA had a markedly higher 30-day risk of bleeding and thrombosis compared to those using VKA both during and after the trial (8,11).

Despite the high incidence of switching in AF patients 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 AF patients switching from VKA to DOAC as well as from DOAC to VKA.

METHODS

Using data from nationwide Danish health registries (as described in detail in the Web Appendix 1), 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 AF patients.

Study design

Patients switching anticoagulant treatment differ from patients not switching (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 (15–17). In acknowledgement hereof, we employed 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 (18). As we aimed to study the association between a transient exposure (switching) and an abrupt onset clinical outcome, we applied the case-crossover design (Web Figure 1) (19). The basic methodology of this design is a 'within-subject' comparison of exposure status (exposed or non-exposed) in the time window leading up to an outcome to exposure status during reference time windows in the past (20), *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 cases were identified consisted of all Danish residents aged ≥ 18 years receiving oral anticoagulant therapy (*i.e.*, VKA or DOAC) for AF during the period August 2011 through December 2018. In Denmark, warfarin accounts for > 95% of the total use of VKA (21). 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 cases, *i.e.*, cohort members with an outcome (see below). Secondly, cases 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 six months leading up to the outcome. Cases with no eligible reference window due to recent cohort entry were excluded from the case-crossover population, as were cases only exposed during the wash-out 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 was 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 one *type* of case-defining outcome, *i.e.*, serve as cases for more than one type of outcome (*e.g.*, 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 that 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 (*i.e.*, VKA or DOAC) of oral anticoagulant than the one most recently filled during the period estimated to be covered by the latter prescription. As 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 four reference windows evenly distributed during the preceding six months (Web Figure 1). We used four reference windows with the intend of improving statistical precision (22). The window between days 31 and 60 before the event was used as a wash-out 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 over time within the study cohort. Incidence rates were estimated for switching from VKA to DOAC and from DOAC to VKA, 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 (ORs) with 95% confidence intervals (CI) for associations between switching from VKA to DOAC and from DOAC to VKA, respectively, 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 OR estimating the underlying incidence-rate ratio of the outcome during exposed vs. unexposed person-time was calculated (20). The ORs were estimated using conditional logistic regression

(conditional on the individual). The OR can be interpreted as an estimate of the 30-day event risk following 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 of exposure assessment (maximum six months), no further confounder adjustment was performed in the main analysis.

Supplementary analyses

We conducted a number of pre-planned subgroup- and sensitivity analyses. The analyses are described in brief below 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, as the very first users of a drug may differ from later users (23–25), we performed a subgroup analysis restricted to DOAC users entering the study cohort from March 1th 2012 and onwards. Fifth, potential time trends in the exposure were accounted for using a case-time control approach (26). This analytical approach is similar to the case-crossover method but adjusts for time-trends estimated in a control population. Finally, we omitted to collapse treatment episodes with <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, TX, USA). The Danish Data Protection Agency approved the study (16/13916). In Denmark, studies based solely on register data do not require ethics committee approval (27).

RESULTS

The study cohort comprised 123,217 oral anticoagulant users with AF (Figure 1) contributing 154,283 treatment episodes. Within the study cohort, switching from VKA to DOAC as well as from DOAC to VKA was very 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 around 60/1000 PY). 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 six 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 1382 (82%) of cases, 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) and more often female (46% vs. 41%) than switchers from DOAC to VKA. Within both switch groups in the case-crossover population, the median age of cases increased from the early to the late part of the study period (from 81 to 84 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 ORs with 95% confidence intervals are provided in Table 1 and Table 2, respectively, as well as in Web Table 5 (site-specific bleeding outcomes). Switching from VKA to DOAC was associated with an increased short-term risk of any bleeding (OR 1.42, 95%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 following 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). Both switching from VKA to DOAC and from DOAC to VKA was associated with an increased short-term risk of death with ORs 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 characteristics were imprecise (Table 1 and Table 2). Although this 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 cases ≥80 years old. As an example, the OR 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 cases >80 years and 1.33 (95%CI: 0.67-2.67) in cases <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 OR 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 period ($OR_{2017-2018}$ 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 following switching from VKA to DOAC, ORs increased when changing the 30-day to a 15-day window; as did the OR for ischemic stroke.

Conversely, ORs 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 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 to the main analysis, the subgroup analysis restricted to cases with at least two consecutive prescriptions of the initial oral anticoagulant produced higher point estimates for almost all outcomes (Table 3). In contrast, the exclusion of cases 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 from OR 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 non-steroidal anti-inflammatory drugs use as well as variables in the CHA_2DS_2-VASc and HASBLED scores, assessed during the observation period. The analysis, which assumes that these variables are not on the causal pathway between switching and outcomes, yielded comparable, although slightly attenuated, risk estimates compared to the main analysis (Table 3).

DISCUSSION

This population-based case-crossover study in AF patients is the first to 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 to 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 due to 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 non-switchers. Further, 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 (28).

Some limitations must be addressed. First, the case-crossover design is vulnerable to time-varying confounding (18). In the context of the present study, this 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 bleedings, could not occur during the observation period, due to the design of the study. Further, 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 discussed further below, 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 (19). 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 employed 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 cases in Denmark, the case-crossover population were relatively small. While not being a source of bias, but rather a result in itself, it 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 following 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 (29,30). Importantly, the risk of intracranial bleeding was not increased in the short-term in the present study. We also observed a nearly two-fold increased ischemic stroke risk following 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. While the increased risk of bleeding could reflect the slower off-set of warfarin than on-set of DOAC resulting in an overlap of anticoagulant effects during switching (2), 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 (30).

Switching from DOAC to VKA following termination of the above mentioned 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 could reflect an overall safe and effective switching regime in Danish clinical practice (31), potentially due to a high quality of anticoagulant control in this setting (32). Also, low median age and prevalence of risk factors in Danish patients switching from DOAC to VKA as previously shown (33), 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 one 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 (30,34). As such, our findings should not be interpreted as evidence of no increased risk of events following 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. While we cannot preclude a minor increased risk of death following 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 following switching would primarily be explained by instability in anticoagulation causing an increased risk of potentially fatal bleedings and/or thrombotic events. However, while 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 cases switched due to accelerating morbidity such as declining renal function and perceived increased risk of bleeding and/or falling (30,33), *i.e.*, factors inherently associated with a short life expectancy. This interpretation is supported by the

modification of these estimates by age, as associations were strongest in cases above 80 years alone.

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 towards the end of the study period. This hypothesis is supported by our finding of the observed increase in the median age of cases 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 had, however, 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 following switching from VKA to DOAC, we overall consider our results as reassuring. Only around 5% of anticoagulated AF patients experiencing an outcome had switched anticoagulant therapy during the preceding six months. This, along with the limited strength of the observed associations indicates that the proportions of bleedings, arterial thromboembolisms, and deaths within the population of AF patients that could be attributed to anticoagulant switching (if the association was causal) are likely very low. Further, in most anticoagulated AF patients, 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-day period following switching from VKA to DOAC. Switching from VKA to DOAC should potentially be considered as an intermittent risk factor of bleeding and ischemic stroke. Overall, switching from DOAC to VKA in AF patients does not appear to be associated with short-term increases in bleeding and ischemic stroke risk in a Danish setting.

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TABLES

Table 1. Associations 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. Overall and Stratified by 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
Subgroup								
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								
<70 years	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 years	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 years	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: CI, confidence interval; DOAC, direct oral anticoagulant; OR, Odds Ratio; VKA, vitamin K antagonist

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

Table 2. Associations 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. Overall and Stratified by 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
Subgroup								
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								
<70 years	0.76	0.34, 1.71	0.93	0.29, 2.99			1.19	0.48, 3.00
70-80 years	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 years	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: CI, confidence interval; DOAC, direct oral anticoagulant; OR, Odds Ratio; VKA, vitamin K antagonist

[a] The top-three 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 due to very low numbers

Table 3. Associations between Oral Anticoagulant Switching and 30-day Risk of Case-Defining Outcomes in Patients with Atrial Fibrillation in Denmark, 2011-2018. Supplementary Analyses.

	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
Analysis																
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																
15 days	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 days	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	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		0.92		1.42		1.81	

apart										0.72, 1.96		0.45, 1.89		0.53, 3.80		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 prior to 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; VKA, vitamin K antagonist

[a] Adjustment for changes in the use of proton pump inhibitors and non-steroidal anti-inflammatory drugs and in the risk scores CHA2DS2-VASc, and HASBLED

FIGURE CAPTIONS

Figure 1. Flow-chart Describing the Selection of the Study Cohort of Atrial Fibrillation (AF) Patients 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.

Figure 2. Incidence Rates of Switching from Vitamin K Antagonists (VKA) to Direct Oral Anticoagulants (DOAC) and from DOAC to VKA among Danish Atrial Fibrillation Patients Using Oral Anticoagulants. Assessed During Each Calendar Quarter of the Study Period (2011-2018).