



Dabigatran and Warfarin for Secondary Prevention of Stroke in Atrial Fibrillation Patients: A Nationwide Cohort Study

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ABSTRACT

BACKGROUND: This register-based observational study compares dabigatran to warfarin for secondary stroke prevention in atrial fibrillation patients among both “new starters” on dabigatran and “switchers” to dabigatran from warfarin.

METHODS: We identified, in nationwide Danish registries, 2398 patients with atrial fibrillation and a history of stroke/transient ischemic attack, making a first-time purchase of dabigatran 110 mg twice a day (bid; D110) and 150 mg bid (D150). Patients were categorized as either vitamin K antagonist (VKA) naive or experienced. Warfarin controls were identified using a complete (for VKA-naive dabigatran patients) or matched sampling approach (for VKA-experienced dabigatran patients). Subjects were followed for an average of 12.6 months for stroke and transient ischemic attacks. Confounder-adjusted Cox regression models were used to compare event rates between treatments.

RESULTS: Among patients with a history of stroke/transient ischemic attack and prior VKA experience, switching to dabigatran was associated with an increased stroke/transient ischemic attack rate for both dabigatran doses compared with continuing on warfarin (D110 hazard ratio [HR] 1.99; 95% confidence interval [CI], 1.42-2.78; D150 HR 2.34; 95% CI, 1.60-3.41). Among prior stroke/transient ischemic attack patients who were new starters on dabigatran or warfarin, the rate of stroke/transient ischemic attack for both doses of dabigatran was similar to or lower than warfarin (D110 HR 0.64; 95% CI, 0.50-0.80; D150 HR 0.92; 95% CI, 0.73-1.15).

CONCLUSIONS: In this register-based study, VKA-experienced patients with a history of stroke or transient ischemic attack who switched to dabigatran therapy had an increased rate of stroke compared with patients persisting with warfarin therapy.

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The risk of stroke in atrial fibrillation patients is high, especially among patients with a history of ischemic stroke or transient ischemic attack.¹ Conventionally, stroke

prevention in atrial fibrillation has involved anticoagulant therapy with vitamin K antagonists (VKA) such as warfarin,² but a narrow therapeutic range makes optimal treatment challenging. Dabigatran etexilate is a direct thrombin inhibitor whose rapid and predictable response can mitigate the complexity of conventional anticoagulant therapy. Trials and subsequent observational studies in mixed patient populations have shown dabigatran to provide comparable or slightly improved protection against stroke and systemic embolism, without compromising bleeding safety.³⁻⁵

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Trial-based findings within the clinically important subgroup of patients with prior stroke have been consistent with the overall efficacy and safety profile results for dabigatran. A predefined sub-study of the Randomized Evaluation of Long Term Anticoagulant Therapy (RE-LY) study found similar or slightly lower rates of stroke and systemic embolism among patients with a prior stroke/transient ischemic attack (2.78% for warfarin, 2.32% for dabigatran 110 mg twice a day [bid]; 2.07% for dabigatran 150 mg bid).⁶ In an indirect comparison of 3 new oral anticoagulants (apixaban, rivaroxaban, and dabigatran) using secondary prevention (previous stroke) trial subgroups,⁷ we found that dabigatran had similar efficacy to warfarin for stroke/systemic embolism, ischemic stroke, and all-cause mortality. However, the extent to which these trial-based subgroup findings transfer to a practical clinical setting is currently unclear.

Analysis of observational data, while insufficient for providing unequivocal treatment recommendations, can provide valuable insight into medication effectiveness in a practical clinical setting. The present nationwide observational study shares design and data similarities with recent studies on myocardial infarction and bleeding risk with dabigatran and warfarin, but in the present study we focus only on patients with previous stroke.^{8,9} Specifically, we used prescription purchase data to assess the effectiveness of dabigatran relative to warfarin for secondary prevention in a real-world atrial fibrillation population with a history of stroke or transient ischemic attack. A substantial proportion of dabigatran initiators are patients who are switched from warfarin – so-called warfarin survivors.¹⁰ In RE-LY, no differences were found in the prognosis between such warfarin survivors and new starters.¹¹ However, this finding may not transfer to a nontrial setting with more autonomous treatment management, particularly not in a high-risk patient group. Accordingly, we assessed the risk of stroke among patients with a history of stroke/transient ischemic attack separately within the stratum of “switchers” from warfarin to dabigatran (compared with warfarin persisters); and within the stratum of “new starters” on dabigatran (compared with new starters on warfarin).

METHODS

We used the civil registration number assigned to all Danish residents to link 3 nationwide databases: 1) the Danish National Prescription Registry,¹² which holds information on purchase date, Anatomical Therapeutic Chemical (ATC)

classification code, and package size for every prescription purchase in Denmark since 1994; 2) the Danish National Patient Register¹³ established in 1977, which includes admission/discharge date and discharge International Classification of Diseases (ICD) diagnoses for >99% of somatic hospital admissions in Denmark; and 3) the Danish Civil Registration System,¹⁴ which holds information on sex, date of birth, vital and emigration status.

Study Population

We identified first-time purchases of dabigatran 110 mg bid (D110) or dabigatran 150 mg bid (D150) during the period August 1, 2011 (dabigatran market entry in Denmark) to May 30, 2013, alongside all purchases of warfarin during the period August 1, 2009 to May 30, 2013 (incorporating predabigatran warfarin purchases in order to determine VKA-experience status). We excluded purchases not preceded by a hospital diagnosis of atrial fibrillation, or preceded by a hospital diagnosis of mitral stenosis, venous thromboembolism, or valvular surgery, or preceded by phenprocoumon use. In accordance with the focus on secondary prevention, we excluded purchases not preceded by a hospital diagnosis of stroke/transient ischemic attack. A person was considered VKA-naive or VKA-experienced if the time since the last warfarin purchase was ≥ 2 years or < 2 years, respectively. A relatively long period was used in order to also reflect naivety in relation to treatment routine.

From the purchase data, we defined a VKA-naive stratum of all VKA-naive subjects making a first-time purchase of dabigatran. As controls in this stratum, we sampled the full population of VKA-naive subjects making a first-time warfarin purchase. The baseline date in the VKA-naive stratum was set to the date of first purchase.

We next defined a VKA-experienced stratum of all VKA-experienced subjects purchasing dabigatran for the first time (switchers). Comparable controls were selected for each switcher by matched sampling among VKA-experienced warfarin controls. Specifically, 2 VKA-experienced warfarin users were matched to each switcher according to calendar month of purchase and duration of VKA experience (up to 1 year; 1-5 years; more than 5 years). The baseline date in the VKA-experienced stratum was set to the date of (first) purchase in the calendar month of inclusion.

Endpoints and Variable Definitions

Participants were followed until July 31, 2013 in the Danish National Patient Register (using the 10th Revision of ICD

CLINICAL SIGNIFICANCE

- In patients with a history of stroke/transient ischemic attack who are VKA-naive, both dabigatran doses provided similar protection to warfarin against recurrent stroke/TIA.
- Vitamin K antagonist-experienced patients with a history of stroke or transient ischemic attack who switch to dabigatran therapy may have an increased rate of a recurrent stroke compared to patients persisting with vitamin K antagonist therapy.
- Caution is recommended when switching prior VKA-experienced atrial fibrillation patients to dabigatran.

codes, ICD-10) for the occurrence of the following endpoints: ischemic stroke (I63, I64.9) or transient ischemic attack (G45); and fatal stroke, not including hemorrhagic stroke (ischemic stroke or transient ischemic attack followed by death within 30 days).

Demographic data were obtained from the Danish Civil Registration System. Comorbidities and co-medications (listed in [Table 1](#)) were ascertained from the Danish National Patient Registry and the Danish National Prescription Registry (for ICD-10 and ATC code definitions, see [Supplementary Table 1](#), available online). We combined covariate information into CHADS₂ (Congestive heart failure, Hypertension, Age 75 years, Diabetes mellitus, and previous stroke or TIA)/CHA₂DS₂VASc (Congestive heart failure, Hypertension, Age 75 years, Diabetes mellitus, previous Stroke/transient ischemic attack, Vascular disease, Age 65-74 years, and Sex category

[female sex]) scores¹⁵ for assessing stroke risk, and a HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile international normalized ratio [INR], Elderly, Drugs/Alcohol) bleeding risk score¹⁶ (definitions in [Supplementary Table 2](#), available online).

Statistical Analysis

Time-to-event analysis was used to compare the risk of stroke/transient ischemic attack between treatment groups within the 2 VKA-experience strata (naive/experienced), measuring risk time from baseline and until the relevant event, emigration, death, or July 31, 2013, whichever came first.

Crude cumulative incidences of stroke/transient ischemic attack were calculated with the Aalen-Johansen method under competing risk of death.¹⁵ Cox regression was used to

Table 1 Participant Characteristics at Baseline, According to VKA-experience Stratum and Current Treatment

	Vitamin K Antagonist-naïve			Vitamin K Antagonist-experienced		
	Warfarin	Dabigatran 110 mg	Dabigatran 150 mg	Warfarin	Dabigatran 110 mg	Dabigatran 150 mg
Subjects, no.	1825	793	646	1918	547	412
Age, years						
Median	76	83	69	75	82	70
Interquartile range	69-82	78-87	64-74	69-82	78-86	65-74
Age ≥65 years, %	84.9	96.1	70.0	85.5	97.3	74.8
Age ≥75 years, %	52.9	82.8	18.6	51.3	84.8	20.9
Female sex, %	44.0	56.2	35.9	38.7	55.0	38.8
Risk scores at baseline						
CHADS ₂ , mean (SD)*	3.15 (0.90)	3.41 (0.79)	2.64 (0.74)	3.19 (0.92)	3.51 (0.79)	2.91 (0.92)
CHA ₂ DS ₂ VASc, mean (SD)†	4.76 (1.40)	5.22 (1.14)	3.87 (1.19)	4.71 (1.33)	5.35 (1.11)	4.34 (1.31)
HAS-BLED, mean (SD)‡	3.11 (1.04)	3.18 (0.89)	2.72 (1.00)	2.81 (0.96)	2.99 (0.95)	2.72 (0.99)
Comorbidities at baseline						
Prior ischemic stroke	75.3	81.2	74.9	75.7	82.1	76.5
Prior transient ischemic attack	36.3	32.0	35.8	37.2	32.4	34.7
Prior bleeding, %	16.2	20.9	13.0	19.2	24.5	19.7
Diabetes, %	16.1	15.4	13.0	18.0	14.1	20.6
Hypertension, %	36.4	33.0	29.6	37.7	36.7	38.1
Abnormal renal function, %	9.5	3.9	0.9	6.0	3.3	3.2
Abnormal hepatic function, %	0.4	0.8	0.0	0.1	0.5	0.0
Prior congestive heart failure, %	9.8	10.2	2.9	11.8	15.5	11.7
Prior myocardial infarction, unstable angina, or cardiac arrest, %	17.6	17.5	8.4	19.8	25.0	22.1
Medications at baseline						
Aspirin, %	43.0	42.7	34.8	23.0	25.6	21.8
Clopidogrel, %	21.4	20.1	20.3	3.0	6.4	5.8
NSAID, %	5.2	4.2	4.8	4.3	4.4	4.9
Clopidogrel and aspirin/NSAID, %	7.7	6.2	5.0	0.4	2.0	1.5

Abbreviations: CHADS₂ = Congestive heart failure, Hypertension, Age 75 years, Diabetes mellitus, and previous stroke or TIA; CHA₂DS₂VASc = Congestive heart failure, Hypertension, Age 75 years, Diabetes mellitus, previous Stroke/transient ischemic attack, Vascular disease, Age 65-74 years, and Sex category (female sex); HAS-BLED = Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol; NSAID = nonsteroidal antiinflammatory drugs; SD = between-subjects standard deviation; VKA = vitamin K antagonist.

*CHADS₂: score ranging from 0-5, which reflects the stroke risk in atrial fibrillation patients not in anticoagulant therapy (see [Supplementary Table 2](#)).
†CHA₂DS₂VASc: score ranging from 0-9, which reflects the risk of stroke in atrial fibrillation patients not in anticoagulant therapy (see [Supplementary Table 2](#)).

‡HAS-BLED: score ranging from 0-9, which reflects the risk of bleeding in atrial fibrillation patients undergoing anticoagulant therapy (see [Supplementary Table 2](#)).

contrast event rates between the dabigatran users and warfarin controls within each of the VKA-experience strata. To address confounding by indication of treatment, regression analyses were adjusted for the baseline values of the following indications: age (continuous; cubic spline); components of CHA₂DS₂VASc and HAS-BLED (binary); and months since August 2011 (continuous; cubic spline). In the VKA-experienced stratum, we also adjusted for time since initiation of VKA therapy (continuous; cubic spline).

We estimated 3-month persistence probabilities,¹⁵ defining time of nonpersistence as the time of treatment switching or >30 days discontinuation (ascertained from previous package sizes and a standard daily dose).

A number of sensitivity/supplementary analyses were carried out. First, we repeated regression analyses after censoring individuals at the time of nonpersistence in order to quantify the effect of continuous treatment (implicitly assuming censoring to be noninformative conditionally on baseline covariates). Second, to assess robustness to a more stringent endpoint definition (with presumably higher validity), regression analyses were also repeated when requiring endpoints to have been registered as the primary diagnosis in connection with hospitalization for at least one night. Lastly, we repeated a subset of the main analyses in the primary prevention group, that is, the analogously defined 2 VKA-experience strata based on the subset of the warfarin/dabigatran purchase data that excluded subjects with a prior diagnosis of stroke/transient ischemic attack.

Stata/MP version 12.1 was used for the statistical analysis (StataCorp LP, College Station, TX). A 2-sided *P* value < .05 was considered as statistically significant.

RESULTS

Study Population Characteristics

A flow chart of the study population is shown in **Figure 1**. In the VKA-naive stratum, we included 1439 patients with atrial fibrillation and a history of stroke/transient ischemic attack making a first-time dabigatran purchase, alongside 1825 patients making a first-time warfarin purchase (controls). In the VKA-experienced stratum, 959 dabigatran switchers were matched to 1918 warfarin controls (selected among 11,159 unique subjects with a total of 76,553 purchases).

Baseline information is shown in **Table 1**. Within each of the VKA-experience strata, D110 users were older, with a median age over 80 years (compared with median ages below 76 and 70 years for warfarin and D150 users, respectively). Accordingly, D110 users also had a higher stroke and bleeding risk (according to CHADS₂/CHA₂DS₂VASc and HAS-BLED scores). There were slightly more females than males in the D110 group (55% to 56%) but not in the D150 and the warfarin group (36% to 44% females). Comparing between VKA-experience strata, the age and sex distribution was similar for each of the 3 treatments. Patients in the VKA-experienced stratum generally had higher CHADS₂/CHA₂DS₂VASc scores

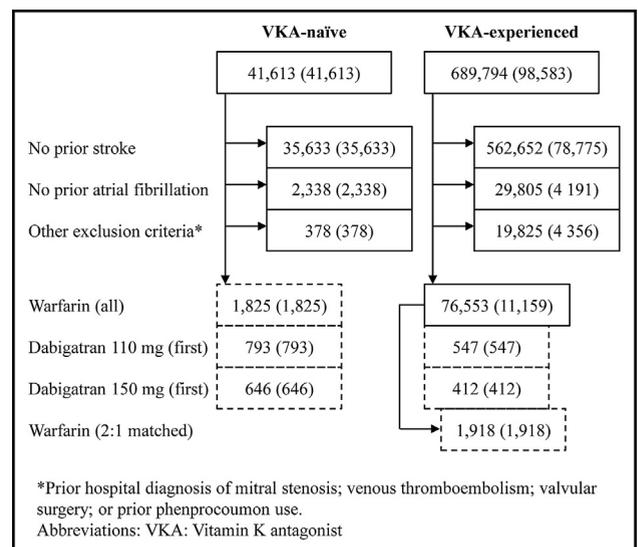


Figure 1 Flow chart showing how the study population was obtained from prescription purchase data. Boxes show number of purchases with number of unique subjects in parentheses. The final study population with prior stroke is displayed in dashed boxes. In the vitamin K antagonist (VKA)-experienced stratum, warfarin purchasers were sampled in a 2:1 ratio for each switcher to dabigatran (according to calendar month of purchase and duration of VKA-experience).

but a similar or slightly decreased HAS-BLED score. There were substantially fewer clopidogrel users in the VKA-experienced stratum (3.0% to 5.8%) compared with the VKA-naive stratum (20.1% to 21.4%), and also fewer aspirin users (21.8% to 23.0%) than in the VKA-naive stratum (34.8% to 43.0%).

Stroke and Transient Ischemic Attacks

The average follow-up time was 12.6 months (SD 4.5 months). Plots of crude cumulative incidences for the composite endpoint of stroke/transient ischemic attack (**Figure 2**) showed that, in the VKA-naive stratum, D110 users had the lowest risk and D150 the highest risk, with the risk increasing more rapidly in the early follow-up period. The stroke risk in the VKA-experienced stratum was lower overall compared with the VKA-naive stratum: within this stratum, warfarin users had the lowest and D110 users the highest risk.

In the VKA-naive stratum (“new starters”), crude annual event rates of stroke/transient ischemic attack ranged from 14.0% to 20.0% (**Table 2**). For the composite endpoint stroke/TIA, adjusted event rates showed a significant 36% reduction among D110 users compared with warfarin (hazard ratio [HR] 0.64; 95% confidence interval [CI], 0.50-0.80), but similar rates for D150 users (HR 0.92; 95% CI, 0.73-1.15). When investigating stroke and transient ischemic attack separately, similar results were found, with slightly larger rate reductions relative to warfarin for the endpoint transient ischemic attack. Crude annual rates

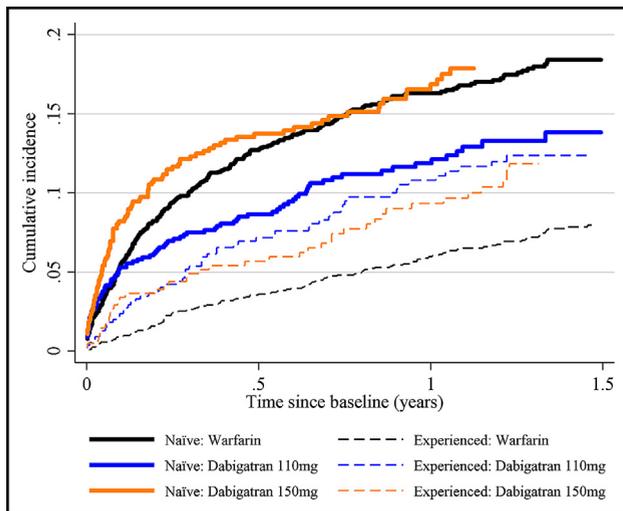


Figure 2 Crude cumulative incidence of the composite endpoint of stroke or transient ischemic attack, according to Vitamin K antagonist-experience and current treatment.

of fatal stroke/transient ischemic attack (not shown in [Table 2](#)) were generally low, ranging from 0.3% to 1.2%.

Turning to the VKA-experienced stratum (“switchers”), crude annual event rates of stroke/transient ischemic attack were overall substantially lower than in the VKA-naïve stratum, ranging from 4.8% to 10.8% ([Table 2](#)). For stroke/TIA, we saw a significant doubling of the event rate for both D110 and D150, compared with warfarin (D110 HR 1.99; 95% CI, 1.42-2.78; D150 HR 2.34; 95% CI, 1.60-3.41). When considering stroke and transient ischemic attack separately, there were comparably sized increases in adjusted rates for dabigatran relative to warfarin. There were again few fatal strokes/transient ischemic attacks (not shown in [Table 2](#)), with crude annual rates ranging from 0.2% for D150 (0.3% for warfarin) to 2.3% for D110.

Treatment Persistence and Supplementary Analyses

Persistence probabilities at 3 months were 87% (warfarin), 79% (D110), and 82% (D150) in the VKA-naïve stratum, and 91% (warfarin), 81% (D110), and 84% (D150) in the VKA-experienced stratum.

The persistence-adjusted Cox regression gave similar results as the main analysis ([Supplementary Table 3](#), available online); the increased rate of stroke/transient ischemic attack with dabigatran relative to warfarin in the VKA-experienced stratum was slightly more pronounced in this analysis (D110 HR 2.33; 95% CI, 1.53-3.55; D150 HR 2.48; 95% CI, 1.53-4.02). Upon censoring patients at time of nonpersistence, crude event rates in the VKA-naïve stratum were increased compared with the main analysis. The results of the second sensitivity analysis, featuring a more restrictive endpoint definition ([Supplementary Table 4](#),

available online), were also consistent with the main analysis, although events rates were low.

Repeating regression analyses in the primary prevention group ([Supplementary Table 5](#), available online) led to similar rates of stroke/transient ischemic attack across strata in the adjusted comparison of D150 versus warfarin (VKA-naïve HR 0.98; 95% CI, 0.72-1; VKA-experienced HR 0.83; 95% CI, 0.51-1.35). In contrast, the rate for D110 was increased compared with warfarin in the VKA-experienced stratum, but not in the VKA-naïve (HR 1.86; 95% CI, 1.30-2.67 and HR 1.01; 95% CI, 0.74-1.37, respectively). Of note, the primary prevention group was substantially younger than the secondary prevention group; and with lower stroke and bleeding risks, according to the CHADS₂/CHA₂DS₂VASc and HAS-BLED scores, respectively ([Supplementary Table 5](#), available online).

DISCUSSION

In this large register-based observational study of secondary stroke prevention among atrial fibrillation patients, we found similar effectiveness of dabigatran relative to warfarin for secondary prevention of stroke/transient ischemic attack among “new starters” on anticoagulant therapy. In contrast, we found a doubling of the stroke/transient ischemic attack rate among “switchers” to both dabigatran doses compared with persisters on warfarin. The overall stroke risk was generally higher in “new starters” on anticoagulant therapy regardless of therapy. A supplementary analysis in the primary stroke prevention group indicated no differences in stroke risk relative to warfarin for both “new starters” and “switchers” on dabigatran, except for switchers to D110 who were at an increased risk of stroke/TIA.

Altogether, our study suggests that caution and vigilance is needed when switching prior VKA-experienced atrial fibrillation patients to dabigatran, especially for patients who are able to consistently maintain a high average time in therapeutic range. The extent to which the increased risk with dabigatran can be attributed to the intervention of switching is, however, not clear, particularly in light of the findings from randomized trials. A predefined sub-study of RE-LY among participants with prior stroke/transient ischemic attack found no significant difference between both dabigatran doses and warfarin in relation to the risk of stroke or systemic embolism.¹⁶

Of note, there were several key differences from the present study: for example, prior VKA experience was not explicitly accounted for, participants were much younger, and recurrent stroke rates were lower. However, in the phase III trial on rivaroxaban versus warfarin,^{17,18} a marked increase in cardiovascular events were seen during the transition to open-label therapy for patients switching therapy at the end of the trial. Meta-analyses and indirect comparisons have thus far confirmed the noninferiority findings from the RE-LY subgroup studies.^{7,19} Divergent findings in an observational study necessitate caution because design limitations can easily induce spurious results. Bias due to

Table 2 Event Rates and Cox Hazard Ratios for the Various Endpoints, According to VKA-experience Stratum and Current Treatment

	No. Events	Rate, % per Year	Crude Hazard Ratio (95% CI)	Adjusted* Hazard Ratio (95% CI)
Vitamin K antagonist-naïve stratum				
Stroke or transient ischemic attack				
Warfarin	300	18.0	1 (reference)	1 (reference)
Dabigatran 110 mg	93	14.0	0.74 (0.59-0.93)	0.67 (0.52-0.86)
Dabigatran 150 mg	102	18.2	0.99 (0.78-1.24)	1.02 (0.80-1.30)
Stroke				
Warfarin	231	13.4	1 (reference)	1 (reference)
Dabigatran 110 mg	82	12.2	0.85 (0.67-1.10)	0.74 (0.56-0.97)
Dabigatran 150 mg	82	14.1	1.02 (0.79-1.31)	1.10 (0.83-1.44)
Transient ischemic attack				
Warfarin	84	4.6	1 (reference)	1 (reference)
Dabigatran 110 mg	17	2.4	0.49 (0.29-0.83)	0.48 (0.28-0.83)
Dabigatran 150 mg	25	4.0	0.85 (0.55-1.34)	0.79 (0.49-1.28)
Vitamin K antagonist-experienced stratum				
Stroke or transient ischemic attack				
Warfarin	133	5.9	1 (reference)	1 (reference)
Dabigatran 110 mg	59	10.8	1.77 (1.30-2.40)	1.54 (1.11-2.13)
Dabigatran 150 mg	45	9.2	1.57 (1.12-2.19)	1.79 (1.25-2.56)
Stroke				
Warfarin	102	4.5	1 (reference)	1 (reference)
Dabigatran 110 mg	52	9.4	2.03 (1.45-2.84)	1.73 (1.21-2.47)
Dabigatran 150 mg	33	6.6	1.49 (1.00-2.20)	1.79 (1.18-2.72)
Transient ischemic attack				
Warfarin	39	1.7	1 (reference)	1 (reference)
Dabigatran 110 mg	14	2.4	1.42 (0.77-2.62)	1.30 (0.68-2.5+)
Dabigatran 150 mg	15	2.9	1.73 (0.95-3.14)	1.72 (0.92-3.22)

Abbreviations: CHA₂DS₂VASc = Congestive heart failure, Hypertension, Age 75 years, Diabetes mellitus, previous Stroke/transient ischemic attack, Vascular disease, Age 65-74 years, and Sex category (female sex); CI = confidence interval; HAS-BLED = Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile international normalized ratio (INR), Elderly, Drugs/Alcohol; VKA = vitamin K antagonist.

*Estimates adjusted for: CHA₂DS₂VASc and HAS-BLED components (binary); age (cubic spline); months since August 2011 (cubic spline); time since initiation of VKA therapy (if applicable; cubic spline).

residual or unmeasured confounding by indication is a serious concern: an apparent treatment effect may simply reflect unaccounted indications for which the treatment was administered. In the present study, clinicians may have been more likely to switch patients with difficulties, maintaining a high time in therapeutic range. Because INR measurements are not available from the registries, we were unable to investigate this. While confounding bias alone is a viable explanation for our findings, it does raise new questions about the sources of such confounding. Indeed, in our analyses, we adjusted for variables that a priori would be expected to be strong confounders, yet we observed only a modest change in the crude point estimates. If confounding bias were to completely explain our findings, we speculate that there would either have to be many unmeasured confounders with a moderate effect or a few very strong unmeasured confounders. As a crude, quantitative assessment, a binary unmeasured confounder with a prevalence of 80% among switchers and 20% among warfarin persisters would only completely explain a Cox model HR of 1.7 if the confounder triples the rate of stroke/transient ischemic attack.²⁰

A combination of confounding bias and (causal) effects due to treatment switching also may explain our divergent

findings. Patients may be less protected in the early period following a switch from warfarin, for example, because of “latent” strokes previously prevented by warfarin and appearing after warfarin discontinuation — or simply because the patient is less familiar with the new treatment. Indeed, plots of crude incidences lend some support to the observation that the early period after switching is a higher-risk period. Lastly, irrespective of whether or not our findings are partly attributable to drug-related causal effects, they still convey the important message that real-world prior stroke/transient ischemic attack “switchers” from warfarin to dabigatran represent a high-risk group. Our study may offer a valuable insight for a future randomized trial of outcomes after treatment switching.

We conclude by commenting on the overall stroke risk differences between VKA-naïve and VKA-experienced users, which are clearly visible in **Figure 2**. These are likely to be attributable to the “healthy user” selection inherent in the definition of the VKA-experienced stratum: to be included in the VKA-experienced stratum, one has to survive the time from treatment initiation to study inclusion with, at most, one stroke. The differences apparent in **Figure 2** emphasize the appropriateness of

treating the VKA-naive and VKA-experienced stratum separately.

Limitations of the present observational study in terms of confounding bias have already been discussed, with the lack of INR measurements being a particular concern. Also, the accuracy of the proposed “intention-to-treat approach” relies on patients actually taking their drugs, as is the case for all comparative effectiveness studies. While the validity of an ischemic stroke diagnosis is high in the Danish Registry of Patients,²¹ misclassification is also a relevant limitation (reassuringly, a more stringent definition of endpoints leads to results consistent with our main analysis). Lastly, one should be aware of the limitations of a comparative effectiveness study of a newly marketed drug such as dabigatran; these can include channeling of selected patient groups toward the new drug, as well as time-varying user population characteristics.²² Strengths of the study include the use of large “real world” atrial fibrillation population, the long follow-up period, and the completeness of the registries.

CONCLUSION

In this nationwide cohort study, we found that for patients with a history of stroke/transient ischemic attack who are VKA-naive, both dabigatran doses provided similar protection to warfarin against recurrent stroke/TIA. Among VKA-experienced patients, the risk of recurrent stroke/transient ischemic attack was significantly increased compared with continued warfarin usage. Although clinical implications from observational data must be drawn carefully, our findings stress the importance of caution and vigilance when switching prior VKA-experienced atrial fibrillation patients to dabigatran, especially for patients with prior good-quality anticoagulation as reflected by a high time in therapeutic range.

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Supplementary Table 1 ICD-10/ATC Codes Used to Identify Comorbid Conditions and Co-medication

Condition	International Classification of Diseases 10th Revision (ICD-10) Code	Anatomical Therapeutic Chemical (ATC) Code
Congestive heart failure	I11.0; I13.0; I13.2; I42.0; I50	and C03C
Left ventricular dysfunction	I50.1; I50.9	
Hypertension		See specified definition* or A10
Diabetes mellitus	E10.0; E10.1; E10.9; E11.0; E11.1; E11.9	
Ischemic stroke	I63; I64.9	
Systemic embolism	I74	
Transient ischemic attack	G45	
Aortic plaque	I70.0	
Peripheral arterial disease	I70.2-I70.9; I71; I73.9	
Myocardial infarction	I21-I23	
Unstable angina	I20	
Cardiac arrest	I46	
Abnormal renal function	I12; I13; N00-N05; N07; N11; N14; N17-N19; Q61	
Abnormal hepatic function	B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85	
Bleeding	I60-I62; D62; J94.2; H11.3; H35.6; H43.1; N02; N95; R04; R31; R58; K25.0; K26.0; K27.0; K28.0; K29.0; S06.3C; S06.4; S06.5; S06.6	
Alcohol intake	E22.4; E52.9A; F10; G31.2; G62.1; G72.1; I42.6; K29.2; K70; K86.0; L27.8A; O35.4M; T51; Z71.4; Z72.1	
Atrial fibrillation	I48	
Medication		
Dabigatran		B01AE07
Warfarin		B01AA03
Aspirin		B01AC06
Clopidogrel		B01AC04
Phenprocoumon		B01AA04
Nonsteroidal antiinflammatory drugs		M01A

*We identified subjects with hypertension from combination treatment with at least 2 of the following classes of antihypertensive drugs:

- I. Alpha adrenergic blockers (C02A, C02B, C02C)
- II. Non-loop diuretics (C02DA, C02L, C03A, C03B, C03D, C03E, C03X, C07C, C07D, C08G, C09BA, C09DA, C09XA52)
- III. Vasodilators (C02DB, C02DD, C02DG, C04, C05)
- IV. Beta-blockers (C07)
- V. Calcium channel blockers (C07F, C08, C09BB, C09DB)
- VI. Renin-angiotensin system inhibitors (C09).

Supplementary Table 2 Definition of Risk Scores

Risk Score	Points, if Present
CHADS₂*	
Congestive heart failure	1
Hypertension	1
Age ≥65 years	1
Diabetes mellitus	1
Stroke (ischemic stroke or transient ischemic attack,)	2
CHA₂DS₂VASc†	
Congestive heart failure or left ventricular dysfunction	1
Hypertension	1
Age ≥65 years	1
Age ≥75 years	1
Diabetes mellitus	1
Stroke (ischemic stroke, transient ischemic disease or systemic embolism)	2
Vascular disease (myocardial infarction, peripheral arterial disease, or aortic plaque)	1
Sex category (female)	1
HAS-BLED‡	
Hypertension	1
Abnormal renal function	1
Abnormal hepatic function	1
Stroke (ischemic stroke or transient ischemic attack)	1
Bleeding	1
Labile international normalized ratio§	1
Elderly age (≥65 years)	1
Drugs (aspirin, clopidogrel, or non-steroidal anti-inflammatory drugs)	1
Alcohol intake	1

Abbreviations: CHADS₂ = Congestive heart failure, Hypertension, Age 75 years, Diabetes mellitus, and previous stroke or TIA; CHA₂DS₂VASc = Congestive heart failure, Hypertension, Age 75 years, Diabetes mellitus, previous Stroke/transient ischemic attack, Vascular disease, Age 65-74 years, and Sex category (female sex); HAS-BLED = Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile international normalized ratio (INR), Elderly, Drugs/Alcohol.

*Reflects stroke risk in atrial fibrillation patients not in anticoagulant therapy (Gage BF, van Walraven C, Pearce L, et al. Selecting patients with atrial fibrillation for anticoagulation: stroke risk stratification in patients taking aspirin. *Circulation*. 2004;110(16):2287-92).

†Reflects stroke risk in atrial fibrillation patients not in anticoagulant therapy (Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest*. 2010;137(2):263-72).

‡Reflects bleeding risk in atrial fibrillation patients undergoing anticoagulant therapy (Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJGM, Lip GYH. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest*. 2010;138(5):1093-100).

§Not included due to unavailable information.

Supplementary Table 3 Persistence-adjusted (Censoring Participants at the Time of Nonpersistence) Event Rates and Cox Hazard Ratios for the Various Endpoints, According to VKA-experience Stratum and Current Treatment

	No. Events	Rate, % per Year	Crude Hazard Ratio (95% CI)	Adjusted* Hazard Ratio (95% CI)
Vitamin K antagonist-naïve stratum				
Stroke or transient ischemic attack				
Warfarin	223	23.2	1 (reference)	1 (reference)
Dabigatran 110 mg	69	17.2	0.73 (0.56-0.95)	0.69 (0.52-0.92)
Dabigatran 150 mg	84	23.9	1.08 (0.84-1.39)	1.13 (0.86-1.49)
Stroke				
Warfarin	174	17.7	1 (reference)	1 (reference)
Dabigatran 110 mg	60	14.8	0.82 (0.61-1.09)	0.75 (0.55-1.03)
Dabigatran 150 mg	66	18.1	1.08 (0.81-1.43)	1.19 (0.87-1.61)
Transient ischemic attack				
Warfarin	55	5.3	1 (reference)	1 (reference)
Dabigatran 110 mg	11	2.6	0.48 (0.25-0.91)	0.50 (0.26-0.96)
Dabigatran 150 mg	21	5.4	1.06 (0.64-1.77)	0.94 (0.55-1.63)
Vitamin K antagonist-experienced stratum				
Stroke or transient ischemic attack				
Warfarin	95	6.8	1 (reference)	1 (reference)
Dabigatran 110 mg	41	12.9	1.82 (1.26-2.63)	1.5 (1.01-2.23)
Dabigatran 150 mg	28	10.3	1.49 (0.98-2.27)	1.67 (1.07-2.61)
Stroke				
Warfarin	73	5.2	1 (reference)	1 (reference)
Dabigatran 110 mg	35	11.0	2.03 (1.36-3.04)	1.59 (1.03-2.45)
Dabigatran 150 mg	21	7.6	1.44 (0.89-2.34)	1.81 (1.08-3.04)
Transient ischemic attack				
Warfarin	23	1.6	1 (reference)	1 (reference)
Dabigatran 110 mg	9	2.7	1.64 (0.76-3.55)	1.59 (0.69-3.69)
Dabigatran 150 mg	8	2.8	1.71 (0.76-3.81)	1.41 (0.61-3.26)

Abbreviations: CHA₂DS₂VASc = Congestive heart failure, Hypertension, Age 75 years, Diabetes mellitus, previous Stroke/transient ischemic attack, Vascular disease, Age 65-74 years, and Sex category (female sex); CI = confidence interval; HAS-BLED = Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile international normalized ratio (INR), Elderly, Drugs/Alcohol; VKA = vitamin K antagonist.

*Estimates adjusted for: CHA₂DS₂VASc and HAS-BLED components (binary); age (cubic spline); months since August 2011 (cubic spline); time since initiation of VKA therapy (if applicable; cubic spline).

Supplementary Table 4 Event Rates and Cox Hazard Ratios for the Various Endpoints, Requiring Endpoints to Have Been Registered as the Primary Diagnosis in Connection with Hospitalization for at Least One Night, According to VKA-experience Stratum and Current Treatment

	No. Events	Rate, % per Year	Crude Hazard Ratio (95% CI)	Adjusted* Hazard Ratio (95% CI)
Vitamin K antagonist-naïve stratum				
Stroke or transient ischemic attack				
Warfarin	97	5.3	1 (reference)	1 (reference)
Dabigatran 110 mg	33	4.6	0.84 (0.56-1.25)	0.69 (0.46-1.03)
Dabigatran 150 mg	23	3.6	0.67 (0.43-1.06)	0.77 (0.48-1.25)
Stroke				
Warfarin	66	3.5	1 (reference)	1 (reference)
Dabigatran 110 mg	26	3.6	0.98 (0.62-1.54)	0.71 (0.45-1.13)
Dabigatran 150 mg	12	1.9	0.51 (0.28-0.95)	0.62 (0.32-1.19)
Transient ischemic attack				
Warfarin	36	1.9	1 (reference)	1 (reference)
Dabigatran 110 mg	9	1.2	0.62 (0.30-1.27)	0.61 (0.30-1.24)
Dabigatran 150 mg	12	1.9	0.95 (0.49-1.83)	0.99 (0.50-1.98)
Vitamin K antagonist-experienced stratum				
Stroke or transient ischemic attack				
Warfarin	59	2.6	1 (reference)	1 (reference)
Dabigatran 110 mg	31	5.5	2.10 (1.36-3.25)	1.49 (0.94-2.36)
Dabigatran 150 mg	20	3.9	1.53 (0.92-2.53)	2.08 (1.20-3.59)
Stroke				
Warfarin	32	1.4	1 (reference)	1 (reference)
Dabigatran 110 mg	23	4.0	2.85 (1.67-4.88)	1.83 (1.04-3.21)
Dabigatran 150 mg	11	2.1	1.55 (0.78-3.07)	2.71 (1.28-5.77)
Transient ischemic attack				
Warfarin	30	1.3	1 (reference)	1 (reference)
Dabigatran 110 mg	9	1.6	1.20 (0.57-2.53)	1.04 (0.47-2.30)
Dabigatran 150 mg	10	1.9	1.48 (0.72-3.03)	1.50 (0.71-3.19)

Abbreviations: CHA₂DS₂VASc = Congestive heart failure, Hypertension, Age 75 years, Diabetes mellitus, previous Stroke/transient ischemic attack, Vascular disease, Age 65-74 years, and Sex category (female sex); CI = confidence interval; HAS-BLED = Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile international normalized ratio (INR), Elderly, Drugs/Alcohol; VKA = vitamin K antagonist.

*Estimates adjusted for: CHA₂DS₂VASc and HAS-BLED components (binary); age (cubic spline); months since August 2011 (cubic spline); time since initiation of VKA therapy (if applicable; cubic spline).

Supplementary Table 5 Event Rates and Cox Hazard Ratios for the Various Endpoints, According to VKA-experience Stratum and Current Treatment, among Atrial Fibrillation Patients with No History of Stroke or Transient Ischemic Attack

	Vitamin K Antagonist-naïve			Vitamin K Antagonist-experienced		
	Warfarin	Dabigatran 110 mg	Dabigatran 150 mg	Warfarin	Dabigatran 110 mg	Dabigatran 150 mg
Subjects, no	9216	2236	3363	6018	1484	1797
Age, years						
Median	72	81	67	74	81	68
Interquartile range	65-79	76-86	62-72	67-80	76-85	64-73
Female sex, %	41.4	54.7	36.7	37.9	54	34.4
Risk scores at baseline						
HAS-BLED, mean (SD)	0.96 (0.88)	1.38 (0.82)	0.61 (0.74)	1.16 (0.90)	1.54 (0.87)	0.91 (0.86)
CHADS ₂ , mean (SD)	2.41 (1.43)	3.15 (1.17)	1.78 (1.19)	2.61 (1.33)	3.35 (1.20)	2.19 (1.28)
CHA ₂ DS ₂ VASc, mean (SD)	1.73 (1.06)	2.01 (0.90)	1.50 (1.02)	1.66 (0.91)	1.94 (0.87)	1.63 (1.00)
Stroke or transient ischemic attack during follow-up						
No. events	194	56	55	98	49	21
Rate, % per year	2.0	2.7	1.7	1.2	3.1	0.9
Crude estimates						
Hazard ratio	1 (reference)	1.31	0.83	1 (reference)	2.47	0.75
95% confidence interval		0.97-1.77	0.61-1.13		1.75-3.48	0.47-1.2
Adjusted* estimates						
Hazard ratio	1 (reference)	0.99	1.05	1 (reference)	1.73	1.04
95% confidence interval		0.72-1.36	0.76-1.45		1.2-2.48	0.64-1.7

CHADS₂: score ranging from 0-5 that reflect the stroke risk in atrial fibrillation patients not in anticoagulant therapy (see [Supplementary Table 2](#)).

CHA₂DS₂VASc: score ranging from 0-9 that reflect the risk of stroke in atrial fibrillation patients not in anticoagulant therapy (see [Supplementary Table 2](#)).

HAS-BLED: score ranging from 0-9 that reflect the risk of bleeding in atrial fibrillation patients undergoing anticoagulant therapy (see [Supplementary Table 2](#)).

Abbreviations: CHADS₂ = Congestive heart failure, Hypertension, Age 75 years, Diabetes mellitus, and previous stroke or TIA; CHA₂DS₂VASc = Congestive heart failure, Hypertension, Age 75 years, Diabetes mellitus, previous Stroke/transient ischemic attack, Vascular disease, Age 65-74 years, and Sex category (female sex); HAS-BLED = Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile international normalized ratio (INR), Elderly, Drugs/Alcohol; SD = between-subjects standard deviation.

*Estimates adjusted for: CHA₂DS₂VASc and HAS-BLED components (binary); age (cubic spline); months since August 2011 (cubic spline); time since initiation of VKA therapy (if applicable; cubic spline).