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ORIGINAL RESEARCH

Association Between Inappropriately Dosed Anticoagulation Therapy With Stroke Severity and Outcomes in Patients With Atrial Fibrillation

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BACKGROUND: Oral anticoagulation (OAC) is effective for stroke prevention in patients with atrial fibrillation. However, some patients experience stroke despite OAC therapy, and knowledge about the impact of prior treatment quality is lacking.

METHODS AND RESULTS: Patients with atrial fibrillation on OAC therapy who had a first-time ischemic stroke were identified in the Danish Stroke Registry (2005–2018). Patients treated with vitamin K antagonist (VKA) therapy were compared according to the international normalized ratio just before stroke (international normalized ratio <2 [subtherapeutic], international normalized ratio 2–3 [therapeutic], international normalized ratio >3 [supratherapeutic]), and patients on underdosed, appropriately dosed, and overdosed direct OAC (DOAC) therapy were compared. Stroke severity was determined using the Scandinavia Stroke Scale (0–58 points), and the risk of very severe stroke (0–14 points) was analyzed by multivariable logistic regression. One-year mortality was determined using multivariable Cox regression. A total of 2319 patients with atrial fibrillation and stroke were included; 1196 were taking a VKA (subtherapeutic [46%], therapeutic [43%], supratherapeutic [11%]), and 1123 were taking DOAC (underdosed [23%], appropriately dosed [60%], and overdosed [17%]). Subtherapeutic and supratherapeutic VKA therapy (compared with therapeutic) and underdosed DOAC therapy (compared with appropriate and underdosed DOAC) patients were older, more often women, and more comorbid. Subtherapeutic VKA therapy was associated with very severe stroke (odds ratio [OR], 2.06 [95% CI, 1.28–3.31]), whereas supratherapeutic VKA therapy was not (OR, 1.24 [95% CI, 0.60–2.57]) compared with therapeutic VKA therapy. Patients on subtherapeutic and supratherapeutic VKA therapy had a higher 1-year mortality (hazard ratio [HR], 1.66 [95% CI, 1.29–2.13]); HR, 1.55 [95% CI, 1.08–2.22], respectively) than those on therapeutic VKA therapy. Treatment with underdosed or overdosed DOAC therapy was not associated with very severe stroke (OR, 1.27 [95% CI, 0.76–2.15]; OR, 0.73 [95% CI, 0.37–1.43], respectively) and was not associated with 1-year mortality (HR, 1.09 [95% CI, 0.83–1.44]; HR, 0.82 [95% CI, 0.57–1.18], respectively) than appropriate DOAC.

CONCLUSIONS: Half of the patients with atrial fibrillation with stroke were on inappropriate OAC therapy. Subtherapeutic VKA was associated with worse stroke severity and higher mortality rate than therapeutic VKA therapy. Neither underdosed nor overdosed DOAC was associated with worse outcomes in adjusted models compared with appropriately dosed DOAC. This study supports DOAC as a first-line therapy over VKA.

Key Words: anticoagulation ■ atrial fibrillation ■ epidemiology ■ inappropriate anticoagulation ■ ischemic stroke

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CLINICAL PERSPECTIVE

What Is New?

- Investigation of appropriateness of prior oral anticoagulation therapy in patients with atrial fibrillation with first-time ischemic stroke with long-term follow-up and the first study with data on direct oral anticoagulants.
- Subtherapeutic vitamin K antagonist therapy was associated with worse stroke severity, and subtherapeutic and supratherapeutic vitamin K antagonist therapies were associated with higher 1-year mortality than therapeutic vitamin K antagonist therapy in adjusted models.
- We found no difference in stroke severity and 1-year mortality between inappropriate and appropriate direct oral anticoagulation therapy in adjusted models.

What Are the Clinical Implications?

- Identification of high-risk patients with atrial fibrillation.
- The data support direct oral anticoagulants as a first-line therapy over vitamin K antagonist.

Nonstandard Abbreviations and Acronyms

DOAC	direct oral anticoagulation
OAC	oral anticoagulation
VKA	vitamin K antagonist

Despite treatment with oral anticoagulation (OAC) therapy, 1% to 2% of patients with atrial fibrillation (AF) still experience stroke annually.[1–5] Previous studies have found an association between subtherapeutic vitamin K antagonist (VKA) therapy and worse stroke severity and higher short-term mortality[2,6–13]; however, contemporary and long-term follow-up data are lacking. Knowledge about the treatment quality of direct OAC (DOAC) (ie, underdosed or overdosed treatment) before stroke has not been investigated and may be a potential reason for DOAC failure.[14]

DOAC therapy has become the standard of care for stroke prevention in patients with AF. However, traditional VKA is still used in many patients worldwide. Appropriate treatment with DOAC is dosed according to age, renal function, body weight, and interacting drugs. In contrast, VKA is dose adjusted to maintain an international normalized ratio (INR) between 2 and 3.[1] Strokes in patients on OAC therapy have been associated with a higher risk of recurrent stroke compared with no OAC therapy[15] and often rule out the use of intravenous thrombolytics.[16] Characterization of the association between inappropriate versus appropriate dosing of OAC and outcomes may help optimize the primary stroke prophylaxis in patients with AF and reduce excess stroke risk.

Accordingly, in this Danish nationwide cohort study, we examined the characteristics, stroke severity, and long-term outcomes of patients with AF according to OAC therapy and the appropriateness of the dosing regimen at the time of admission for stroke.

METHODS

Data Sources

In Denmark, a public health care system enables nationwide health care studies based on the personal identification number that all citizen are given at birth or immigration.[17] The diagnosis of acute stroke was obtained from the Danish Stroke Registry (2003 onward) and have a sensitivity of 97% and a positive predictive value of 90%.[18] The diagnosis of prior AF, in the absence of valvular heart diseases and prior heart valve surgery, were found in the Danish Patient Registry (1978 onward).[19] The National Prescription Registry provided information on redeemed prescriptions since 1995.[20] Vital status was drawn from the Danish Civil Registration System and date of death from The Danish Registry of Causes of Death. Data on INR and creatinine were obtained from electronic registries from laboratories of hospitals in 4 out of 5 regions in Denmark and general practitioners in the Capital Region of Denmark. The *International Classification of Diseases, Eighth Revision* and *Tenth Revision* (*ICD-8; ICD-10*) and *Anatomical Therapeutic Chemical Classification System* codes used are shown in Table S1. No raw data are accessible by law. The corresponding author can provide details of the analyses on request.

Study Population

Patients were included if they were admitted with first-time ischemic stroke or unspecified stroke and a history of AF at any time before admission for stroke (ie, index date). We included patients from January 1, 2005 to ensure higher data completeness in the Danish Stroke Registry. Hereafter, stroke refers to a group of both ischemic and unspecified strokes. Previously, Krarup et al found that two-thirds of unspecified strokes registered in the Danish National Patient Registry were ischemic strokes and were therefore included.[21] Patients without a filled prescription for either a VKA (warfarin or marcoumar) or DOAC (dabigatran, rivaroxaban, apixaban, or edoxaban) up to 90 days before the stroke were excluded. Patients on VKA therapy without an INR value measured

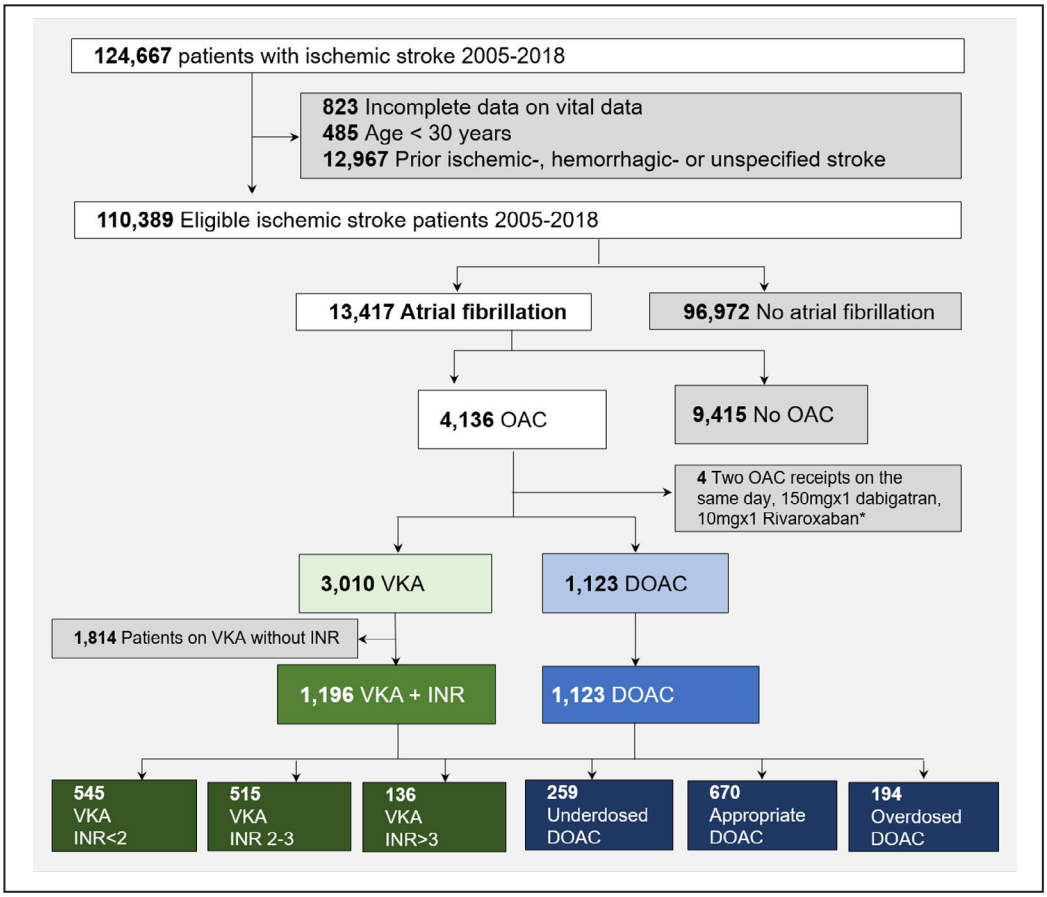

Figure 1. Selection of the study population.
DOAC indicates direct oral anticoagulation, INR, international normalized ratio; OAC, oral anticoagulation; and VKA, vitamin K antagonist. *Patients prescribed dabigatran 150 mg or rivaroxaban 10 mg were excluded because these doses are typically given after orthopedic procedures.

≤30 days before the stroke or on the day of hospitalization were also excluded (Figure 1).

Covariates

Baseline concomitant pharmacotherapy, apart from anticoagulation therapy, was defined as redeemed prescriptions ≤180 days before the index date. Information on comorbidities was obtained any time before the index admission from the Danish National Patient Registry. Information on smoking status, type of residence, civil status, thrombolysis, and thrombectomy were obtained from the Danish Stroke Registry. Modified CHA_2DS_2–VASc (congestive heart failure, hypertension, age ≥75 years [doubled], diabetes, history of stroke/transient ischemic attack/systemic arterial thromboembolism [doubled], vascular disease, age 65–74 years, and sex category [women]), and HAS-BLED (hypertension, abnormal renal or liver function, stroke, bleeding history, labile INR, elderly [age >65 years], drug consumption, or alcohol abuse) scores were calculated as described previously.[22,23] The estimated glomerular filtration rate was calculated using the chronic kidney disease–epidemiology collaboration equation on an individual basis using creatinine values measured within 3 years before the stroke.

Exposure—Appropriateness of Oral Anticoagulation Therapy

Patients on VKA therapy were categorized according to the latest INR value within 30 days before stroke or on the day of admission: INR <2 (subtherapeutic), INR 2 to 3 (therapeutic), INR >3 (supratherapeutic). The dose reduction criteria applied in this study were based on recommendations from the European Society of Cardiology, Danish national guidelines, and data availability (ie, we did not have data on body weight and creatinine values for all patients).[1] The criteria are displayed in Table S2. Underdosed DOAC therapy was defined as low-dose DOAC without guideline recommendations justifying this. Overdosed DOAC therapy was defined as high-dose DOAC therapy despite fulfilling the guideline criteria for low-dose DOAC. Inappropriate DOAC was defined as either underdosed or overdosed DOAC.

Outcomes

The primary outcome was stroke severity acquired from the Danish Stroke Registry determined on admission and graded according to the Scandinavian Stroke Scale based on 9 different parameters: speech (10–0 points), orientation (6–0 points), facial palsy (2–0 points), consciousness (6–0 points), eye movement (4–0 points), gait (12–0 points) and hand, arm, and leg motor power (6–0 points each). The Scandinavian Stroke Scale can be categorized into very severe stroke (0–14 points), severe stroke (15–29 points), moderate stroke (30–44 points), and mild stroke (45–58 points).[24] The Scandinavian Stroke Scale is equally as good as the National Institutes of Health Stroke Scale in predicting mortality and disability.[25–27] The secondary outcome was 1-year all-cause mortality. Patients were followed from the date of stroke admission until the occurrence of death or the end of the study (December 31, 2019), whichever came first.

Statistical Analysis

Baseline characteristics were described as frequencies and percentages and medians with 25th to 75th percentiles. Covariates were compared using the χ^2 test for categorical variables and the Kruskal-Wallis test for continuous variables. Differences within groups were tested using the Cochran-Mantel-Haenszel test.

The odds ratio (OR) of very severe stroke (0–14 points) versus the composite of mild, moderate, and severe stroke (15–58 points) was analyzed for patients on VKA therapy (VKA with INR 2–3 [reference], VKA INR <2, VKA INR >3) and DOAC therapy (appropriate DOAC [reference], underdosed DOAC, overdosed DOAC) in 2 separate multivariable logistic regression models. The models were adjusted for age, sex, calendar year, diabetes, chronic kidney disease, transient ischemic attack/thromboembolism, ischemic heart disease, chronic obstructive lung disease, cancer, peripheral artery disease, heart failure, prior bleeding, liver disease, hypertension, dementia, alcohol abuse, and prior use of statins, aspirin, nonsteroidal anti-inflammatory drugs, and adenosine diphosphate receptor inhibitors. Patients with missing Scandinavian Stroke Scale values were excluded from the analysis. Interaction with age, sex, and calendar year were tested, and no clinically meaningful interactions were found. Continuous variables were tested for linearity.

The cumulative incidence of 1-year mortality (including in-hospital mortality) was assessed using the Kaplan-Meier method, and differences were tested using the log-rank test. The relative rate of mortality associated with OAC treatment quality was determined using a multivariable Cox proportional hazards model and adjusted for the same factors as the multivariable logistic regression models. The Cox models were tested for the proportional hazards assumption and linearity of continuous variables. The interaction between exposure and age, sex, and calendar year on the outcome were tested, and no clinically meaningful interactions were found. A 2-sided P value of <0.05 was considered statistically significant. Numbers ≤3 are not reported because of local data protection regulations. All analyses were performed using SAS statistical software (version 9.4; SAS Institute, Cary, NC).

Sensitivity Analysis

We performed several sensitivity analyses to test the robustness of our findings.

1. Categorization of patients on DOAC into underdosed, overdosed, and appropriately dosed were analyzed in a sensitivity analysis with the original guideline criteria (Table S2). As such, we included all patients on DOAC with an available creatinine value within the past 3 years before the stroke, and for patients on apixaban and edoxaban, a body weight estimate (from index stroke admission) was also required.
2. In a sensitivity analysis of patients on apixaban, the effect of applying 1 of 2 criteria for dose reduction was assessed compared with applying 2 of 2 criteria.
3. The analyses were repeated on a population, excluding all patients with unspecified strokes.
4. We performed a sensitivity analysis excluding all patients on VKA before the first DOAC was approved in Denmark (August 22, 2011).

Ethics

In Denmark, no ethical approval is needed for registry-based research, because individuals cannot be identified in the data. The Danish Data Protection Agency approved this study (approval number: P-2019-191).

RESULTS

Baseline Characteristics

There were 13 417 patients with AF admitted with stroke (2005–2018), of whom 4136 (30.8%) were treated with OAC. After the last exclusion criteria were applied, 2319 patients were included: 1196 patients on VKA and 1123 on DOAC. Data on the duration of OAC therapy and switching of OAC therapy before stroke are shown in Table S3. Of all strokes included, 2205 patients had an ischemic stroke (97.9% and 92.5% in the VKA and DOAC groups, respectively), and 114

had an unspecified stroke (2.1% and 7.5% in the VKA and DOAC groups, respectively). The baseline characteristics of the patients on VKA and DOAC overall are shown in Table S4.

Baseline Characteristics of Patients on VKA

In total, 545 (45.6%) patients on VKA had an INR <2, 515 (43.1%) had an INR between 2 and 3, and 136 (11.4%) had an INR >3. The median INR of all patients on VKA was 2.0 (25th–75th percentile, 1.5–2.6), and the majority of INR values were either measured at the index date for stroke (52.3%) or the day before (38.1%).

Overall, patients on sub- or supratherapeutic VKA therapy were more often women, slightly older, more comorbid, and more often on concomitant therapy with aspirin than those on therapeutic VKA therapy (Table). Among all patients on VKA, 245 (20.7%) patients were included before 2010, when recommendations of VKA to patients with AF were included in the European Society of Cardiology guidelines.[28]

Baseline Characteristics of Patients on DOAC

The majority of patients on DOAC were appropriately dosed (670 patients [59.7%]), whereas 259 (23.1%) were underdosed, and 194 (17.3%) were overdosed. The distribution of different specific DOAC drugs is shown in Table S5. Patients on underdosed DOAC were more likely to be women and more comorbid, were a median of 8 to 9 years older, were more often living alone, and more often at a care home than patients who were on appropriately dosed DOAC and overdosed DOAC (Table).

Outcome

Stroke Severity Among Patients on VKA

The proportion of patients with very severe stroke was higher for patients on subtherapeutic VKA therapy (68 [13.5%]) and supratherapeutic VKA therapy (12 [9.6%]) than therapeutic VKA therapy (30 [6.2%]) (Figure 2A). In the adjusted models, subtherapeutic VKA therapy was associated with a higher likelihood of very severe stroke (OR, 2.06 [95% CI, 1.28–3.31]), but for supratherapeutic VKA therapy, the association was nonsignificant (OR, 1.24 [95% CI, 0.60–2.57]) (Figure 3A).

Stroke Severity Among Patients on DOAC

Patients on underdosed DOAC were more likely to have very severe stroke than those on appropriate and overdosed DOAC therapy (32 [12.8%], 54 [8.3%], 13 [6.8%], respectively) (Figure 2B). After adjustment, the estimates became nonsignificant for patients on underdosed DOAC (OR, 1.27 [95% CI, 0.76–2.15]) and overdosed DOAC (OR, 0.73 [95% CI, 0.37–1.43]) (Figure 3B).

Mortality Among Patients on DOAC

The absolute risk and relative mortality rates were higher for patients on subtherapeutic VKA than for therapeutic VKA (absolute risk difference 15.3% [P<0.01]; hazard ratio [HR], 1.66 [95% CI, 1.29–2.13]). The absolute risk and relative mortality rates were also higher for patients on supratherapeutic VKA than those on therapeutic VKA (absolute risk difference 13.0% [P<0.01]; HR, 1.55 [95% CI, 1.08–2.22]) (Figure 4A).

Mortality Among Patients on DOAC

The absolute 1-year mortality was significantly higher for patients on underdosed DOAC compared with appropriate DOAC (risk difference of 10.9% [P<0.01]) but became nonsignificant in adjusted models (HR, 1.09 [95% CI, 0.83–1.44]). The absolute and relative 1-year mortality rates were lower for patients on overdosed DOAC compared with appropriate DOAC, but statistically nonsignificant (risk difference of 5.7% [P = 0.09]; HR, 0.82 [95% CI, 0.57–1.18]) (Figure 4B).

Sensitivity analysis

1. First, we included all patients on DOAC with an available creatinine value, and for apixaban and edoxaban also an available body weight estimate, and analyzed the appropriateness of the DOAC dose using the original dose-reduction criteria (Table S2). In total, 53 (15.1%) were underdosed, 211 (59.9%) were appropriately dosed, and 88 (25.0%) were overdosed according to the guideline-specific criteria. The baseline characteristics were similar; however, outcome analyses were limited by power (Table S6 and Figure S1).
2. Second, we tested the categorization of apixaban patients according to dose reduction criteria requiring 1 of 2 criteria instead of 2 of 2 criteria for dose reduction. Applying 1 of 2 criteria for dose reduction categorized 21 (5.5%) patients as underdosed, 270 (70.5%) patients as appropriately dosed, and 92 (24.0%) as overdosed.
3. Third, we conducted a sensitivity analysis excluding 114 patients (4.9%) with unspecified stroke and found similar results to the main analysis. Among patients on VKA, 502 (45.4%) had an INR <2, 479 (43.3%) had an INR between 2 and 3, and 125 (11.3%) had an INR >3. Among patients on DOAC, 253 (23.0%) were underdosed, 654 (59.5%) were appropriately dosed, and 192 (17.5%) were overdosed.

Table. Baseline Patient Characteristics of Patients on VKA Stratified Upon INR and DOAC Stratified Upon Underdosed, Appropriate, and Overdosed Treatment

Variable	VKA INR <2	VKA INR 2–3	VKA INR >3	Underdosed DOAC	Appropriate DOAC	Overdosed DOAC
No. (%)	545 (45.6)	515 (43.1)	136 (11.4)	259 (23.1)	670 (59.7)	194 (17.3)
Sex (men)	283 (51.9)	322 (62.5)	74 (54.4)	95 (36.7)	374 (55.8)	111 (57.2)
Median age, y, 25th–75th percentile	80 (73–86)	79 (73–84)	81 (75–85)	85 (79–89)	77 (71–83)	76 (70–82)
Comorbidities, n (%)						
Diabetes	114 (20.9)	90 (17.5)	29 (21.3)	46 (17.8)	137 (20.4)	39 (20.1)
Hypertension	410 (75.2)	362 (70.3)	97 (71.3)	156 (60.2)	445 (66.4)	150 (77.3)
Alcohol abuse	20 (3.7)	10 (1.9)	7 (5.1)	17 (6.6)	39 (5.8)	19 (9.8)
Prior bleeding	156 (28.6)	138 (26.8)	35 (25.7)	82 (31.7)	163 (24.3)	51 (26.3)
Cancer	145 (26.6)	113 (21.9)	29 (21.3)	57 (22.0)	169 (25.2)	36 (18.6)
Congestive heart failure	190 (34.9)	157 (30.5)	53 (39.0)	90 (34.7)	184 (27.5)	55 (28.4)
Chronic kidney disease	61 (11.2)	47 (9.1)	13 (9.6)	5 (1.9)	52 (7.8)	27 (13.9)
TIA/TE	89 (16.3)	80 (15.5)	33 (24.3)	39 (15.1)	81 (12.1)	14 (7.2)
COPD	88 (16.1)	81 (15.7)	26 (19.1)	47 (18.1)	108 (16.1)	28 (14.4)
PAD	46 (8.4)	47 (9.1)	21 (15.4)	25 (9.7)	52 (7.8)	18 (9.3)
Ischemic heart disease	203 (37.2)	198 (38.4)	58 (42.6)	101 (39.0)	220 (32.8)	71 (36.6)
Concomitant medication, n (%)						
Acetylsalicylic acid	98 (18.0)	61 (11.8)	24 (17.6)	32 (12.4)	75 (11.2)	36 (18.6)
ADP inhibitors	11 (2.0)	8 (1.6)	≤3	20 (7.7)	25 (3.7)	7 (3.6)
NSAID	49 (9.0)	41 (8.0)	10 (7.4)	18 (6.9)	64 (9.6)	28 (14.4)
Diuretics*	356 (65.3)	312 (60.6)	81 (59.6)	145 (56.0)	355 (53.0)	117 (60.3)
Digoxin	188 (34.5)	201 (39.0)	50 (36.8)	97 (37.5)	208 (31.0)	61 (31.4)
Verapamil	71 (13.0)	55 (10.7)	13 (9.6)	9 (3.5)	33 (4.9)	6 (3.1)
Statins	208 (38.2)	201 (39.0)	46 (33.8)	95 (36.7)	248 (37.0)	81 (41.8)
HAS-BLED score						
0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	≤3	0 (0.0)
1	12 (2.2)	12 (2.3)	4 (2.9)	4 (1.5)	19 (2.8)	0 (0.0)
2	80 (14.7)	99 (19.2)	30 (22.1)	64 (24.7)	165 (24.6)	10 (5.2)
≥3	453 (83.1)	404 (78.4)	102 (75.0)	191 (73.7)	485 (72.4)	184 (94.8)
CHA_2DS_2-VASc score						
0	4 (0.7)	4 (0.8)	≤3	≤3	13 (1.9)	0 (0.0)
1	20 (3.7)	28 (5.4)	≤3	6 (2.3)	52 (7.8)	6 (3.1)
≥2	521 (95.6)	483 (93.8)	133 (97.8)	252 (97.3)	605 (90.3)	188 (96.9)
Smoking						
Smoker	60 (14.1)	73 (17.2)	25 (21.0)	31 (15.4)	103 (17.9)	45 (26.5)
Former smoker, >0.5 y	161 (37.8)	164 (38.7)	51 (42.9)	80 (39.8)	253 (43.9)	63 (37.1)
Never	205 (48.1)	187 (44.1)	43 (36.1)	90 (44.8)	220 (38.2)	62 (36.5)
Civil status						
Cohabiting	275 (51.3)	315 (62.6)	67 (52.3)	81 (31.8)	359 (54.6)	107 (55.4)
Alone	246 (45.9)	177 (35.2)	58 (45.3)	163 (63.9)	274 (41.6)	80 (41.5)
Other	15 (2.8)	11 (2.2)	≤3	11 (4.3)	25 (3.8)	6 (3.1)
Type of residence						
Own residence	491 (92.1)	472 (93.5)	123 (95.3)	212 (83.1)	595 (90.7)	180 (93.8)
Care home	34 (6.4)	27 (5.3)	6 (4.7)	43 (16.9)	58 (8.8)	11 (5.7)
Other	8 (1.5)	6 (1.2)	0 (0.0)	0 (0.0)	≤3	≤3
Thrombolysis†						
Yes	36 (7.6)	≤3	0 (0.0)	7 (2.7)	23 (3.5)	6 (3.2)
No	40 (8.4)	44 (9.4)	17 (13.8)	≤3	6 (0.9)	≤3

(*Continued*)

Table. Continued

Variable	VKA INR <2	VKA INR 2–3	VKA INR >3	Underdosed DOAC	Appropriate DOAC	Overdosed DOAC
Contraindicated	400 (84.0)	420 (90.1)	106 (86.2)	245 (96.1)	636 (95.6)	181 (95.8)
Thrombectomy†						
Yes	18 (4.9)	10 (2.6)	≤3	10 (3.9)	31 (4.7)	11 (5.8)
No	17 (4.6)	16 (4.2)	6 (7.1)	4 (1.6)	8 (1.2)	≤3
Not indicated	331 (90.4)	354 (93.2)	76 (89.4)	241 (94.5)	625 (94.1)	175 (92.6)
eGFR, mL/min per 1.73 m^2						
≥90	43 (11.3)	48 (14.2)	9 (8.3)	≤3	52 (17.6)	22 (25.6)
60–89	156 (40.8)	162 (47.8)	43 (39.8)	44 (35.5)	147 (49.7)	33 (38.4)
30–59	157 (41.1)	118 (34.8)	50 (46.3)	72 (58.1)	90 (30.4)	30 (34.9)
15–29	23 (6.0)	9 (2.7)	5 (4.6)	5 (4.0)	6 (2.0)	≤3
<15	≤3	≤3	≤3	0	≤3	0

ADP indicates adenosine diphosphate; COPD, chronic obstructive lung disease; DOAC, direct oral anticoagulation; eGFR, estimated glomerular filtration rate; HAS-BLED, hypertension, abnormal renal or liver function, stroke, bleeding history, labile international normalized ratio, elderly (age >65 years), drug consumption or alcohol abuse; INR, international normalized ratio; NSAID, nonsteroidal anti-inflammatory drugs; PAD, peripheral artery disease; TIA/TE, transient ischemic attack/thromboembolism; and VKA, vitamin K antagonist.

*Diuretics: loop diuretics, non-loop diuretics, thiazide, spironolactone, diuretics in combination (*Anatomical Therapeutic Chemical Classification System* codes C07C, C08G, C03B, C03X).

†Registered from September 2011 onward. Missing (n): smoking (403), civil (46), type of residence (49), thrombolysis (145), thrombectomy (379), eGFR (984).

4. Fourth, we excluded all patients on VKA before August 22, 2011. There were 799 patients who experienced a stroke treated with VKA, and 348 (43.6%) had an INR <2, 370 (46.3%) had an INR between 2 and 3, and 81 (10.1%) had an INR >3. Outcomes on stroke severity (Table S7) and mortality (Figure S2) were comparable to the main analysis.

DISCUSSION

This study examined the characteristics of patients with ischemic stroke and prior AF on inappropriate versus appropriate OAC therapy in a real-world setting and yielded 3 major findings. First, patients on sub- or supratherapeutic VKA therapy were slightly older, were more likely to be women, and had a higher comorbidity burden than patients on therapeutic VKA. Patients on underdosed DOAC were older, more likely to be women, and were more comorbid than patients on appropriate or overdosed DOAC. Second, subtherapeutic VKA therapy was associated with worse stroke severity in absolute and relative numbers than therapeutic VKA therapy. This difference was not found between inappropriate and appropriate DOAC therapy after adjustment for baseline covariates. Third, subtherapeutic and supratherapeutic VKA therapy was associated with higher 1-year mortality compared with therapeutic VKA therapy. This difference in mortality was not found among patients receiving inappropriate versus appropriate DOAC therapy.

To our knowledge, this is the first study to describe the appropriateness of prior VKA and DOAC treatment in patients with first-time ischemic stroke with long-term follow-up. Previous observational studies and clinical trials[2,6–9,13,29–32] included patients with a history of prior stroke/transient ischemic attack, yet different mechanisms and risk factors exist in this patient group.[33] Furthermore, this heterogeneous study population is not optimal for the characterization of stroke patients on OAC therapy. This lack of knowledge is supported by a systematic review of the literature by Meinel et al.[14] Many studies have examined the risk of stroke according to OAC therapy. However, by looking at prior OAC therapy in patients who present with stroke potential, preventable strokes might be identified. Of all patients with first-time ischemic stroke, 30.8% were on prior OAC treatment, which is comparable to what was found by Gundlund et al and Gadsbøll et al.[34,35] Of the patients on VKA, 57% had an INR out of range before stroke, and 40.4% of the patients on DOAC were inappropriately dosed.

Patient Characteristics

In line with prior studies, we found that patients on therapeutic VKA were only slightly younger than patients on subtherapeutic and supratherapeutic VKA.[7,9,11,13] Additionally, we found that stroke in patients on underdosed DOAC were 8 to 9 years older than patients on appropriate and overdosed DOAC. This has only been described in a much younger Asian study population by Jung et al.[36] As in previous studies,[2,7] we also found a higher proportion of women among subtherapeutic and supratherapeutic patients on VKA. However, Sakamoto et al found fewer women among patients on subtherapeutic VKA therapy.[6] In this study, we also found a higher

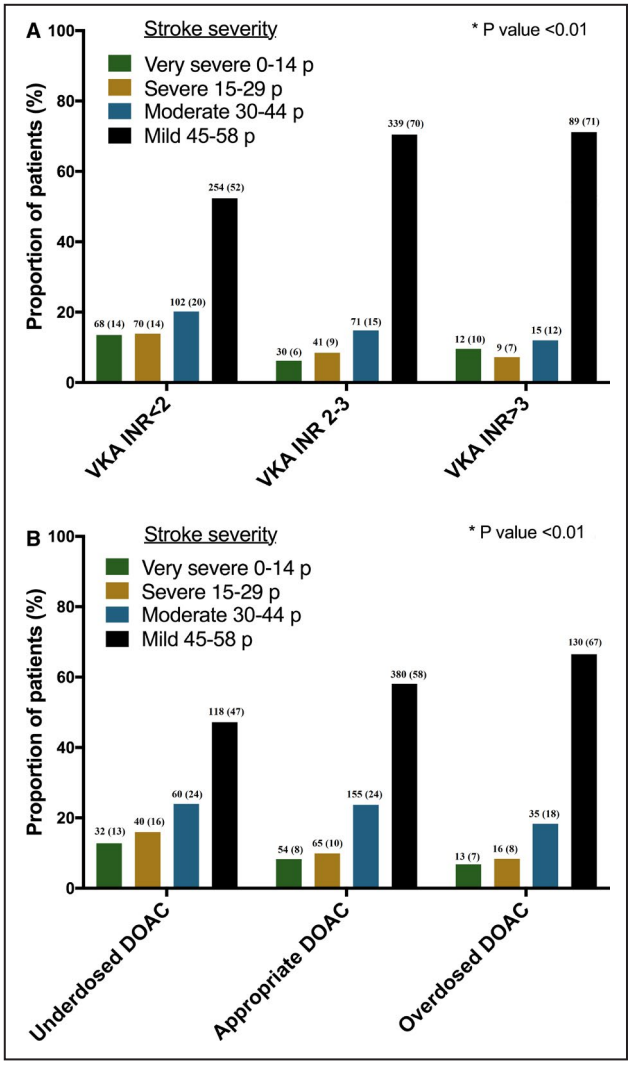

Figure 2. Stroke severity among patients on vitamin K antagonist (VKA) and direct oral anticoagulants (DOAC). **A,** Median Scandinavian Stroke Scale (SSS): VKA with international normalize ratio (INR) <2 (46.0 [25th–75th percentile, 26.0–54.0]), INR 2 to 3 (51.0 [25th–75th percentile, 42.0–56.0]), INR >3 (51.0 [25th–75th percentile, 42.0–56.0]). **B,** Median SSS: Underdosed DOAC (43.0 [25th–75th percentile, 26.0–52.0]), appropriate DOAC (48.0 [25th–75th percentile, 36.0–55.0]), overdosed DOAC (51.0 [25th–75th percentile, 41.0–55.0]). Missing on SSS: VKA (86 [7.2%]) and DOAC (28 [2.5%]); p indicates points. *Cochran-Mantel-Haenszel test.

proportion of women among patients on underdosed DOAC, but not among patients on overdosed DOAC, which was not found by Jung et al.[36] Patients on subtherapeutic and supratherapeutic VKA were more comorbid compared with patients on therapeutic VKA in the present study. However, other studies did not find this clear contrast in comorbidity burden among patients on VKA.[2,7–9,13,29,37] This study additionally describes that patients on underdosed DOAC were older and more often comorbid women than patients on appropriate and overdosed DOAC. Patients on

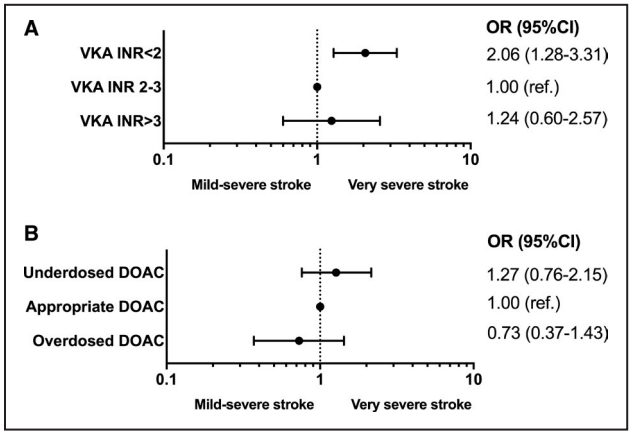

Figure 3. Multivariable logistic regression model. Odds ratio (OR) of very severe stroke among patients on vitamin K antagonist (VKA) (**A**) and patients on direct oral anticoagulation (DOAC) (**B**). Scandinavian Stroke Scale: Very severe stroke (0–14 points), mild-severe stroke (15–58 points). INR indicates international normalized ratio.

overdosed DOAC were more like patients on appropriate DOAC but were slightly more comorbid.

Stroke Severity

Subtherapeutic VKA therapy, rather than therapeutic VKA therapy, was associated with worse stroke severity in the adjusted models. Prior studies found that patients on therapeutic VKA therapy were associated with lower stroke severity, measured on the National Institutes of Health Stroke Scale compared with subtherapeutic VKA therapy.[2,6,8–13] However, Indredavik et al found no significant difference in stroke severity among patients on VKA with an INR of <2 and ≥2.[38]

In the present study, underdosed or overdosed DOAC was not significantly associated with very severe stroke in the adjusted models. Jung et al found, in a Korean population, lower stroke severity among patients on underdosed DOAC compared with standard dose DOAC, yet they were limited by power.[36]

Mortality

In our study, we found that inappropriate versus appropriate VKA therapy at the time of stroke was associated with higher 1-year mortality. However, among patients on DOAC, this difference did not hold true in adjusted models, because it was largely explained by patients on inappropriate therapy being older and/or with more comorbidities.

Most of the existing literature only reports in-hospital mortality or mortality as a part of the modified Rankin Scale, and most studies are limited by power.[2,7–9,13] Xian et al found higher in-hospital mortality, and Schwammenthal et al found a higher risk of 1-year mortality (nonsignificant in adjusted models) for

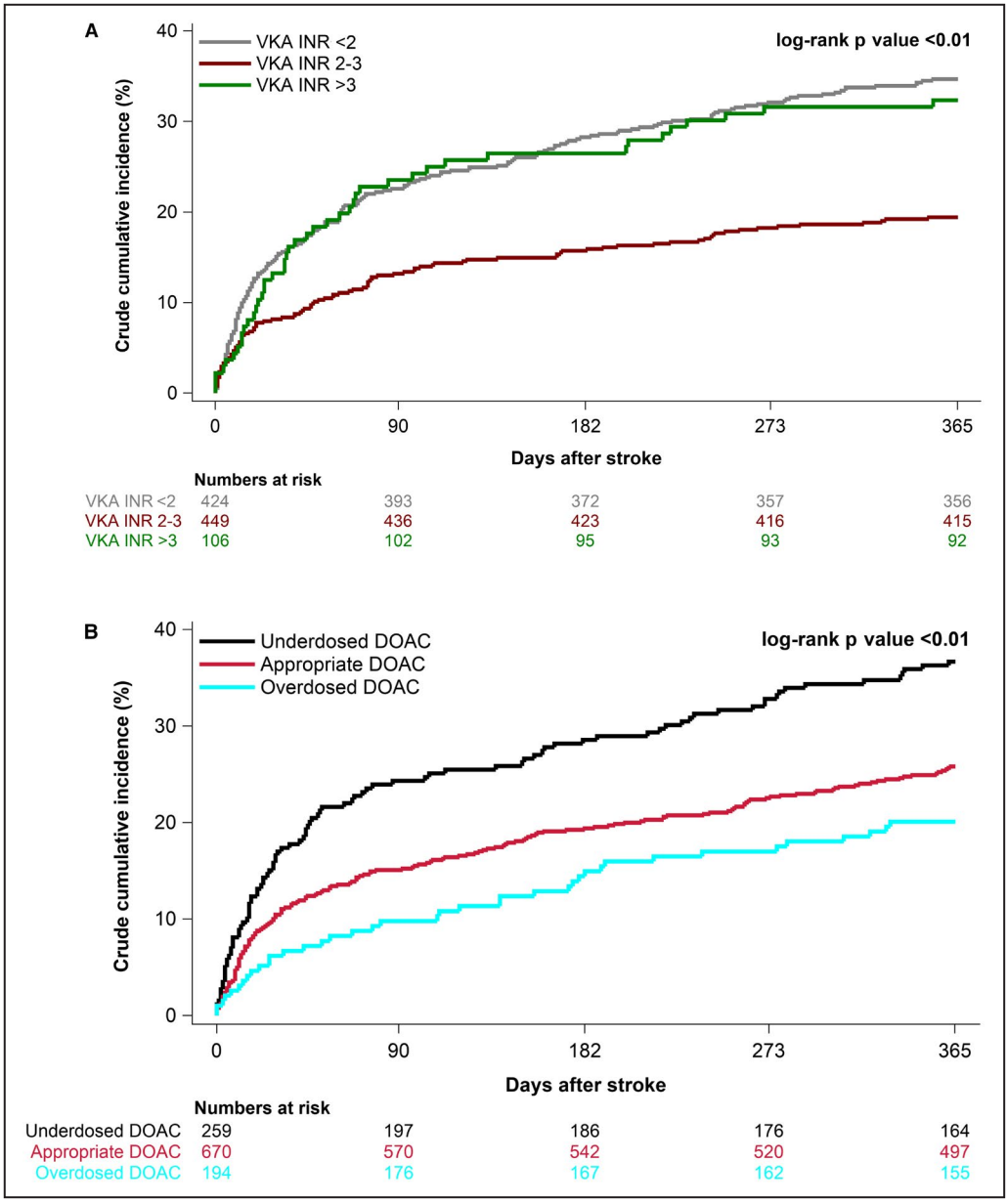

Figure 4. Cumulative incidence of 1-year mortality and adjusted hazard ratio (HR) among patients on vitamin K antagonist (VKA) and direct oral anticoagulation (DOAC).
A, VKA: VKA INR <2: (34.7% [95% CI, 30.7–38.7]),* adjusted HR, 1.66 (95% CI, 1.29–2.13); VKA INR 2 to 3: (19.4% [95% CI, 16.1–22.9]), reference; VKA INR >3: (32.4% [95% CI, 24.6–40.3]),† adjusted HR, 1.55 (95% CI, 1.08–2.22). **P*<0.01. †*P*<0.01. **B**, DOAC: Underdosed DOAC: (36.7% [95% CI, 30.8–42.5]),‡ adjusted HR, 1.09 (95% CI, 0.83–1.44); Appropriate DOAC: (25.8% [95% CI, 22.6–29.2]), reference; Overdosed DOAC: (20.1% ([95% CI, 14.8–26.0]),{} adjusted HR 0.82 (95% CI, 0.57–1.18). ‡*P* <0.01. {}*P*=0.09. INR indicates international normalized ratio.

patients on VKA, with INR <2, compared with VKA, with INR ≥2.[2,11] Patients on underdosed or overdosed DOAC compared with appropriately dosed DOAC were not associated with a higher rate of 1-year mortality in adjusted models.

The reasons for inappropriate VKA therapy are probably not the same as those for inappropriate DOAC therapy; this will also affect characteristics and outcomes. Nevertheless, this study supports the clinical guidelines in recommending DOAC as first-line therapy over VKA.

Limitations

This was an observational study using nationwide real-world data enabling the characterization of patients outside a clinical trial setting. However, this

type of study only describes associations; residual bias cannot be precluded, and there might be risk of confounding by indication in a population who already have experienced a stroke. The different DOAC groups and VKA groups have different distribution of age and sex, and we cannot fully elucidate the effect of age and sex on the association with the outcome. This is an inherent limitation of the study design.

Of the entire study population, 4.9% had an unspecified stroke, and based on Krarup et al, around one-third of these may be hemorrhagic strokes.[21] Because we did not have information on body weight and creatinine values for all patients, we had to modify the guideline-specific dose-reduction criteria for DOAC. However, we conducted a sensitivity analysis of 25% of the patients on DOAC who had a creatinine value within 3 years before stroke and body weight estimates and yielded similar results. We used creatinine values taken within 3 years before stroke to avoid too much missing data. In the main analysis for apixaban, we choose to apply 2 of 2 criteria for dose reduction, instead of 1 of 2 criteria, as is recommended by Alexander et al.[39]

CONCLUSIONS

Approximately half of the included patients with AF, who experienced an ischemic stroke on OAC therapy, were on inappropriately dosed therapy. Patients who were on subtherapeutic VKA treatment just before the stroke had a higher associated stroke severity and higher rate of 1-year mortality compared with patients on therapeutic VKA. Among patients treated with underdosed or overdosed DOAC than appropriately dosed DOAC, no association with more severe strokes and higher 1-year mortality was found after adjustment for baseline characteristics. This study supports DOACs as a first-line therapy over VKA.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S7
Figures S1–S2

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Supplemental Material

Content

Supplementary Table S1. Diagnoses and pharmacotherapy used for defining the population

Atrial fibrillation or atrial flutter	*Presence of:* *ICD10*: I48 *ICD8:* 427.93, 427.94 Primary and secondary diagnoses and in- and outpatient contacts excluding diagnoses given at the emergency department. *Absence of:* *ICD8*: 4240, 4241, 39500- 39502, 39508, 39509, 39600-39604, 39608, 39609 *ICD10:* Z952, Z954, I05, I06, I080A, I081A, I082A, I083A *NCSP:* KFKD, KFKH, KFMD, KFMH, KFGE, KFJF	
Ischemic stroke	Registered in the Danish Stroke Registry; Ischemic stroke or unspecified stroke.	
Prior ischemic-, hemorrhagic and unspecified stroke.	Found in the Danish Patient Registry. ICD10: I60-I64, ICD8: 430, 431, 433, 434, 436. Primary and secondary diagnose and in-hospital diagnoses.	
Comorbidities *Primary and secondary diagnoses. In-hospital (full day hospitalization) and out-hospital contacts.*		
Alcohol abuse	Defined from diagnosis and adverse alcohol consumption during hospitalization and prescription of anti-alcohol addiction medication	*ICD10*: F10, K70, E52, T51, K860, E244, G312, I426, O354, Z714, Z721, G621, G721, K292, L278A *ICD8*: 303 *ATC*: N07BB
Bleeding history	Defined from diagnosis of hemopericardium, respiratory or urinary tract bleeding, bleeding in the eye, gastrointestinal bleeding, intradural bleeding (not hemorrhagic stroke), retroperitoneal bleeding, hemothorax, spinal cord hemorrhage, anemia due to bleeding, traumatic subdural and subarachnoid bleeding.	*ICD10*: D62, D500, I312, N02, R31, R04, H313, H356, H431, H450, H052A, K228F, K250, K252, K254, K256, K260, , K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K298A, K625, K638B, K638C, K661, K838F, K868G, K920, K921, K922, I850, I864A, S064, S065, S066, G951A S368D, J942, D500, D62, M321B *ICD8*: 280.01, 531.90, 531.92, 531.95, 532.90, 533.90, 534.90, 535.01, 569.15

Chronic kidney disease	Defined from diagnosis	*ICD10*: E102, E112, E132, E142, I120, M321B, M300, M313, M319, M321B, N02-N08, N11-N12, N14, N18-19, N26, N158-N160, N162-N164, N168, Q61, Z992 *ICD-8:* 403, 404, 581-584, 753.10, 753.11, 753.19
Diabetes mellitus	Defined from treatment	*Treatment*: ATC A10
Heart failure	Defined from diagnosis	*ICD10*: I110, I130, I132, I42, I43, I50 *ICD8:* 427.09, 427.10, 427.11, 427.19, 428.99
Hypertension	Defined from combination treatment with a least two classes of antihypertensive drugs. This definition of hypertension has a positive predictive value of 80.0% and a specificity of 94.7%.[22]	*Treatment*: Adrenergic α-antagonist, non-loop-diuretics, loop-diuretics, vasodilators, beta blockers, calcium channel blockers, and renin-angiotensin system inhibitors.
Ischemic heart disease	Defined from diagnosis	*ICD10*: I20-I25 *ICD8*: 410-414
Liver disease	Defined from diagnoses of liver cancer, chronic liver disease, cirrhosis, and hepatitis	*ICD10*: B15-B19, C22, K70-K77, Z944, I982B, D684C *ICD8:* 571-573, 155, 070
Peripheral artery disease	Defined from diagnosis	*ICD10*: I70 *ICD8:* 440, 444
Vascular disease	Defined from diagnoses of ischemic heart disease and peripheral artery disease	
Chronic obstructive lung disease	Defined from diagnoses	*ICD10:* DJ42-44 *ICD8:* 490-492, 515-518
Cancer	Defined from diagnoses	*ICD10:* DC00-DC97 *ICD8:* 140-199, 200-207
Transient ischemic attach/thromboembolism	Defined from diagnoses	*ICD10:* G458, G459, I26, I74 *ICD8:* 435, 437, 438, 444, 450
Dementia	Defined from diagnoses	*ICD10:* F00-F03, G30, F051, G311 *ICD8*: 290.09, 290.10

CHA_2DS_2-VASc	Defined from diagnoses above	Heart failure: 1 point Hypertension: 1 point Age≥75: 2 points Diabetes: 1 point Stroke/transient ischemic attach/thromboembolism: 2 points Vascular disease 1 point 65≤ age <75: 1 point Female sex: 1 point
HAS-BLED	Defined from diagnoses above	Age >65: 1 point Hypertension: 1 point Chronic kidney disease: 1 point Liver disease: 1 point Stroke: 1 point Prior bleeding: 1 point ASA or ADP inhibitors or Dipyridamole or NSAID: 1 point Alcohol abuse: 1 point
Medication		
Oral anticoagulants	ATC codes	Warfarin: B01AA Marcoumar: B01AA04 Dabigatran: B01AE07 Rivaroxaban: B01AF01 Apixaban: B01AF02 Edoxaban: B01AF03

ICD8: 8th revision of the International Classification of Diseases system

ICD10: 10th revision of the International Classification of Diseases system.

NCSP: The Nordic Medical Statistics Committees Classification of Surgical Procedures

Supplementary Table S2: Modified and original dose reduction criteria applied in the study

	Main analysis – modified dose reduction criteria	**Sensitivity analysis** - original guideline criteria
Dabigatran 110 mg BID	One of following: - Age ≥ 80 years - Concomitant use of verapamil - HAS-BLED score≥3 - Diagnose of chronic kidney disease	One of following: - Age ≥ 80 years - Concomitant use of verapamil - HAS-BLED score≥3 - eGFR 30-50 ml/min/1.73m^2 *
Rivaroxaban 15 mg OD	Diagnose of chronic kidney disease	eGFR 15-49 ml/min/1.73m^2 †
Apixaban 2.5 BID	2 of 2 criteria: - Age ≥ 80 years - Diagnose of chronic kidney disease	2of 3 criteria: - Age ≥80 years - Body weight ≤60 kg - creatinine ≥133 μmol/L
Edoxaban 30 mg OD	One of the following: - Diagnose of chronic kidney disease - Concomitant glycoprotein inhibitors (ciclosporin, dronedarone, erythromycin, ketokonazol)	One of the following: - GFR 15-50 ml/min/1.73m^2 * - Body weight ≤60 kg - Concomitant glycoprotein inhibitors (ciclosporin, dronedarone, erythromycin, ketokonazol)

* Including all with eGFR ≤50 ml/min/1.73m^2. †Including all with eGFR ≤49 ml/min/1.73m^2. eGFR; Estimated glomerular filtration rate. OD; Once daily, BID; Bis in die ie. Twice a day. HAS-BLED score (hypertension, abnormal renal- or liver function, stroke, bleeding history, labile international normalized ratio, elderly [age>65 years], drug consumption or alcohol abuse). CHA2DS2-VASc (congestive heart failure, hypertension, age ≥75 years[doubled], diabetes mellitus, prior transient ischemic attack or thromboembolism [doubled], vascular disease, age 65–74 years, sex category).

Supplementary Table S3: Switch of oral anticoagulation before stroke and type of oral anticoagulation therapy (OAC) 3-9 month prior to stroke according to study groups

Switch of OAC within 3 months before stroke, N(%).	**Percentage of the patients who were prescribed the same OAC drug 3-9 months prior to stroke, N (%).**
VKA • Prior DOAC: 10 (0.8%) Dabigatran: • Prior DOAC: 4 (0.1%) • Prior VKA: 9 (2.6%) Rivaroxaban: • Prior DOAC: ≤3 • Prior VKA: 11 (3.0%) Apixaban: • Prior dabigatran: 8 (2.1%) • Prior VKA: 9 (2.3%) Edoxaban • Prior DOAC ≤3 • Prior VKA: ≤3	Dabigatran: 304 (83.3%) Rivaroxaban: 277 (76.5%) Apixaban: 284 (74.2%) Edoxaban: 0 (0%) VKA: 1077 (90.1)

VKA: Vitamin K antagonist, DOAC: Direct oral anticoagulant.

Supplementary Table S4: Baseline characteristics of patients on vitamin K antagonist (VKA) and direct oral anticoagulant therapy (DOAC).

Variable	VKA	DOAC
N (%)	1123 (48.4)	1196 (51.6)
Sex (men)	580 (51.6)	679 (56.8)
Median age, years (25^{th}-75^{th} percentile)	78 (72, 85)	79 (73, 85)
Comorbidities (%)		
Diabetes	222 (19.8)	233 (19.5)
Hypertension	751 (66.9)	869 (72.7)
Alcohol abuse	75 (6.7)	37 (3.1)
TIA/Thromboembolism	142 (12.6)	186 (15.6)
Prior bleeding	296 (26.4)	329 (27.5)
Cancer	262 (23.3)	287 (24.0)
Congestive heart failure	329 (29.3)	400 (33.4)
Chronic kidney disease	84 (7.5)	121 (10.1)
Chronic obstructive lung disease	183 (16.3)	195 (16.3)
Peripheral artery disease	95 (8.5)	114 (9.5)
Ischemic heart disease	392 (34.9)	459 (38.4)
Concomitant medicine, (%)		
Acetylsalicylic acid	143 (12.7)	183 (15.3)
ADP inhibitors	52 (4.6)	21 (1.8)
Non-Steroidal Anti-Inflammatory Drugs	110 (9.8)	100 (8.4)
Diuretics*	617 (54.9)	749 (62.6)
Digoxin	366 (32.6)	439 (36.7)
Verapamil	48 (4.3)	139 (11.6)
Statins	424 (37.8)	455 (38.0)
HAS-BLED score		
0	≤3	0 (0.0)
1	23 (2.0)	28 (2.3)
2	239 (21.3)	209 (17.5)
≥3	860 (76.6)	959 (80.2)
CHA2DS2-VASc score		
0	13 (1.2)	7 (0.6)
1	60 (5.3)	50 (4.2)
≥2	1050 (93.5)	1139 (95.2)
Smoking		
Smoker	179 (18.9)	158 (16.3)
Former smoker (>0.5 year)	396 (41.8)	376 (38.8)
Never	372 (39.3)	435 (44.9)
Civil status		

Co-habiting	547 (49.5)	657 (56.3)
Alone	517 (46.7)	481 (41.2)
Other	42 (3.8)	29 (2.5)
Type of residence		
Own residence	987 (89.5)	1,086 (93.1)
Care home	112 (10.2)	67 (5.7)
Other	4 (0.4)	14 (1.2)
Thrombolysis†		
Yes	36 (3.2)	38 (3.6)
No	11 (1.0)	101 (9.5)
Contraindicated	1062 (95.8)	926 (86.9)
Thrombectomy†		
Yes	52 (4.7)	31 (3.7)
No	15 (1.4)	39 (4.7)
Not indicated	1041 (94.0)	761 (91.6)
eGFR, ml/min/1.73m^2		
≥90	119 (17.0)	148 (13.9)
60-89	313 (44.6)	416 (39.1)
30-59	230 (32.8)	373 (35.1)
15-29	31 (4.4)	88 (8.3)
<15	9 (1.3)	39 (3.7)

TIA: Transient ischemic attach. ADP-inhibitors: Adenosine diphosphate receptor inhibitors. *Diuretics: loop diuretics, non-loop diuretics, thiazide, spironolactone, diuretic combi (ATC code C07C, C08G, C03B, C03X). HAS-BLED score (hypertension, abnormal renal- or liver function, stroke, bleeding history, labile international normalized ratio, elderly [age>65 years], drug consumption or alcohol abuse). CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years[doubled], diabetes mellitus, prior TIA or thromboembolism[doubled], vascular disease, age 65–74 years, sex category). †Registered from September 2011 and onwards. eGFR: estimated glomerular filtration rate. Missing (N): Smoking (403), civil (46), type of residence (49), thrombolysis (145), thrombectomy (379), eGFR (553).

Supplementary Table S5. Distribution of specific DOAC drugs among underdosed, appropriate and overdosed DOAC patients.

Variable	Underdosed DOAC	Appropriate DOAC	Overdosed DOAC	Total
Dabigatran, N(%)	11 (4.3)	181 (27.0)	173 (89.2)	365 (32.5)
Rivaroxaban, N(%)	112 (43.2)	240 (35.8)	10 (5.2)	362 (32.2)
Apixaban, N(%)	132 (51.0)	240 (35.8)	11 (5.7)	383 (34.1)
Edoxaban, N(%)	4 (1.5)	9 (1.3)	0	13 (1.2)
DOAC: Direct oral anticoagulant				

Supplementary Table S6: Sensitivity analysis with patients on direct oral anticoagulant (DOAC) with available creatinine and weight estimates values for dose reduction criteria.

Variable	Underdosed DOAC	Appropriate DOAC	Overdosed DOAC
N(%)	53 (15.1)	211(59.9)	88(25.0)
Sex (men)	19 (35.8)	114 (54.0)	54 (61.4)
Median age, years (25^{th}-75^{th} percentile)	82 [77, 87]	78 [73.0, 83.5]	74.5 [70, 82]
Comorbidities, N(%)			
Diabetes	11 (20.8)	40 (19.0)	13 (14.8)
Hypertension	30 (56.6)	138 (65.4)	66 (75.0)
Alcohol abuse	5 (9.4)	17 (8.1)	11 (12.5)
TIA/Thromboembolism	6 (11.3)	28 (13.3)	9 (10.2)
Abnormal Liver function	≤3	≤3	4 (4.5)
Prior bleeding	19 (35.8)	59 (28.0)	24 (27.3)
Cancer	10 (18.9)	53 (25.1)	22 (25.0)
Congestive heart failure	15 (28.3)	71 (33.6)	23 (26.1)
Chronic kidney disease	4 (7.5)	10 (4.7)	4 (4.5)
Chronic obstructive lung disease	12 (22.6)	35 (16.6)	13 (14.8)
Peripheral artery disease	6 (11.3)	12 (5.7)	8 (9.1)
Ischemic heart disease	21 (39.6)	79 (37.4)	27 (30.7)
Concomitant medication, N(%)			
Acetylsalicylic acid	6 (11.3)	23 (10.9)	9 (10.2)
ADP inhibitors	4 (7.5)	4 (1.9)	≤3
Non-Steroidal Anti-Inflammatory Drugs	4 (7.5)	20 (9.5)	12 (13.6)
Diuretics*	25 (47.2)	111 (52.6)	53 (60.2)
Digoxin	19 (35.8)	62 (29.4)	26 (29.5)
Verapamil	≤3	16 (7.6)	7 (8.0)
Statins	21 (39.6)	73 (34.6)	34 (38.6)
HAS-BLED score			
0	0 (0.0)	0 (0.0)	0 (0.0)
1	≤3	5 (2.4)	0 (0.0)
2	16 (30.2)	48 (22.7)	7 (8.0)
≥3	36 (67.9)	158 (74.9)	81 (92.0)
CHA_2DS_2-VASc score			
0	0 (0.0)	4 (1.9)	0 (0.0)
1	≤3	16 (7.6)	≤3
≥2	51 (NA)	191 (90.5)	86 (NA)
Smoking			
Smoker	4 (11.4)	28 (16.8)	17 (22.7)
Former smoker (>0.5 year)	16 (45.7)	82 (49.1)	28 (37.3)

Never	15 (42.9)	57 (34.1)	30 (40.0)
Civil status			
Co-habiting	19 (35.8)	111 (53.6)	46 (52.9)
Alone	34 (64.2)	87 (42.0)	37 (42.5)
Other	0 (0.0)	9 (4.4)	4 (4.6)
Type of residence			
Own residence	45 (86.5)	192 (92.8)	80 (93.0)
Care home	7 (13.2)	15 (7.1)	5 (5.7)
Other	0 (0.0)	0 (0.0)	≤3
Thrombolysis†			
Yes	3 (5.7)	11 (5.3)	≤3
No	≤3	≤3	0 (0.0)
Contraindicated	49 (92.5)	196 (94.2)	84 (98.8)
Thrombectomy†			
Yes	≤3	13 (6.2)	4 (4.7)
No	≤3	≤3	0 (0.0)
Not indicated	50 (94.3)	194 (93.3)	81 (95.3)
eGFR, ml/min/1.73m^2			
≥90	≤3	36 (17.1)	22 (25.0)
60-89	24 (45.3)	105 (49.8)	30 (34.1)
30-59	28 (52.8)	65 (30.8)	36 (40.9)
15-29	0 (0.0)	5 (2.4)	0 (0.0)
Scandinavian Stroke Scale			
Median, years (25th-75th percentile)	33 (22-54)	49 (31-55)	49 (42-55)
OR (95%CI) 'Very severe stroke'	1.22 (0.43-3.42)	1.00	0.28 (0.07-1.16)

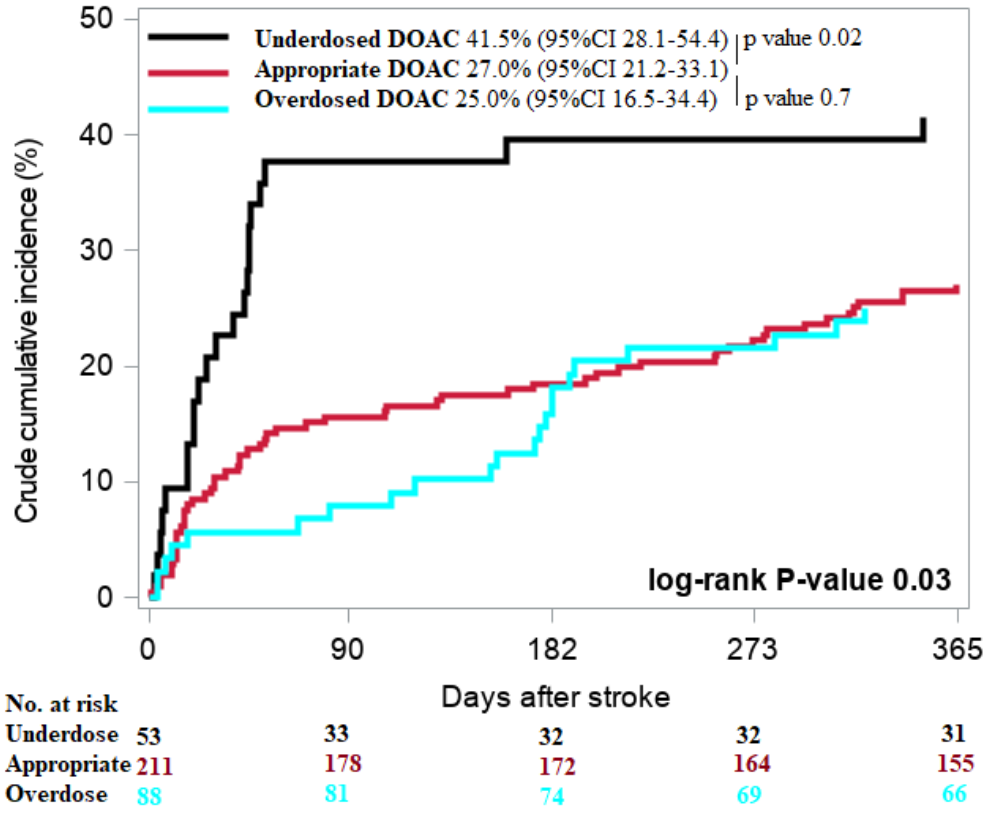
TIA: Transient ischemic attach. ADP inhibitors: ADP-inhibitors: Adenosine diphosphate receptor inhibitors, OR: Odds ratio. *Diuretics: loop diuretics, non-loop diuretics, thiazide, spironolactone, diuretic combi (ATC code C07C, C08G, C03B, C03X). HAS-BLED score (hypertension, abnormal renal- or liver function, stroke, bleeding history, labile international normalized ratio, elderly [age>65 years], drug consumption or alcohol abuse). CHA2DS2-VASc (congestive heart failure, hypertension, age ≥75 years[doubled], diabetes mellitus, prior TIA or thromboembolism[doubled], vascular disease, age 65–74 years, sex category). †Registered from September 2011 and onwards. eGFR: estimated glomerular filtration rate. Missing (N): Smoking (75), civil (5), type of residence (7), thrombolysis (6), thrombectomy (6)
No patients on edoxaban had body weight registered as such patients on edoxaban was not included in this analysis.

Supplementary Table S7: Stroke severity among a subpopulation of patients on vitamin K antagonist treatment included from 22nd of August 2011

Variable	INR <2	INR 2-3	INR>3
Very severe stroke	50 (14.9%)	23 (6.4%)	12 (15.4%)
Severe stroke	46 (13.7%)	32 (8.7%)	6 (7.7%)
Moderate stroke	63 (18.8%)	50 (13.9%)	11 (14.1%)
Mild stroke	177 (52.7%)	256 (70.9%)	49 (62.8%)

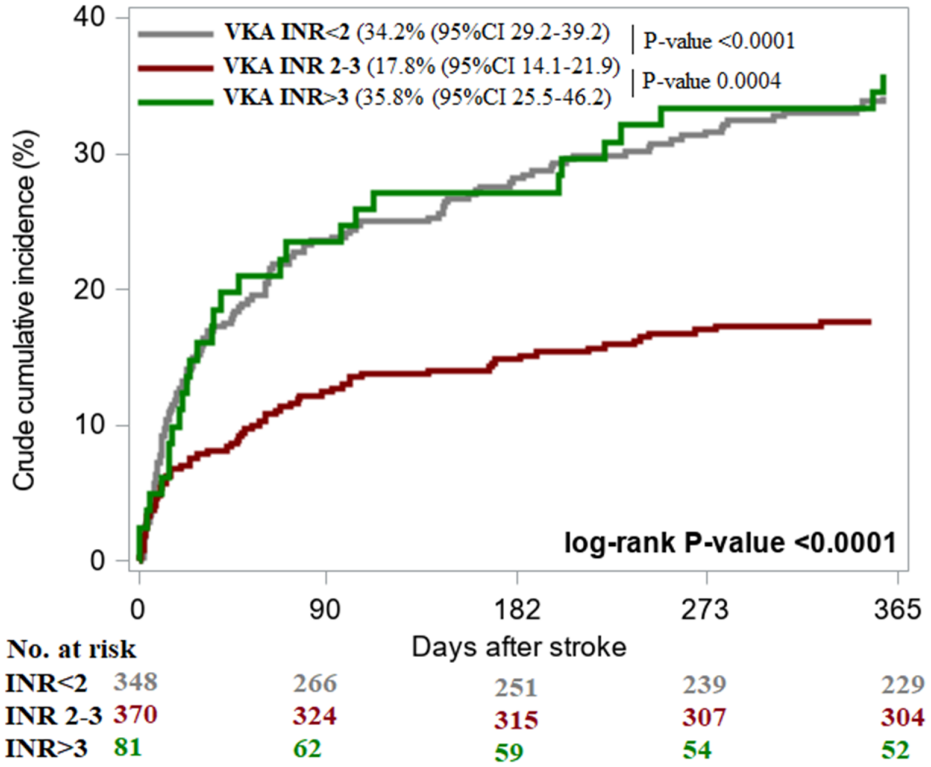
Stroke severity categories according to the Scandinavian Stroke Scale (missing, N: 24). INR: international normalized ratio.

Supplementary Figure S1: Sensitivity analysis with patients on direct oral anticoagulation (DOAC) therapy with available creatinine and weight estimates values for dose reduction criteria. 1-year mortality and adjusted hazard ratio (HR).



Underdosed DOAC, Adjusted HR: 1.09 (95%CI 0.76-1.78)
Overdosed DOAC, Adjusted HR: 0.82 (95%CI 0.57-1.18)
Appropriate DOAC: Reference

Supplementary Figure S2: Cumulative incidence of one-year mortality including patients on vitamin K antagonist (VKA) treatment from 22nd of August 2011



VKA INR <2, Adjusted HR: 1.80 [95%CI 1.32-2.45]
VKA INR >3: Adjusted HR: 1.93 [95%CI 1.24-3.02]
VKA INR 2-3: Reference
INR: international normalized ratio