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CLINICAL RESEARCH
Atrial fibrillation

Non-vitamin K-dependent oral anticoagulants have a positive impact on ischaemic stroke severity in patients with atrial fibrillation

Simon Hellwig[1,2], Ulrike Grittner[1,3], Heinrich Audebert[1,2], Matthias Endres[1,2,4,5,6], and Karl Georg Haeusler[1,2]*

[1]Center for Stroke Research Berlin, Charité - Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany; [2]Department of Neurology, Charité - Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany; [3]Department of Biostatistics and Clinical Epidemiology, Charité - Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany; [4]Berlin Institute of Health, Kapelle-Ufer 2, 10117 Berlin, Germany; [5]German Center for Neurodegenerative Diseases (DZNE), Partner Site Berlin, Germany; and [6]German Center for Cardiovascular Diseases (DZHK), Partner Site Berlin, Germany

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Aims Several studies showed reduced stroke severity in patients with atrial fibrillation (AF) if the international normalized ratio (INR) was ≥2 at stroke onset. There are no respective data for non-vitamin K-dependent oral anticoagulants (NOACs). The aim of this study was to compare the impact of NOAC or phenprocoumon intake on stroke severity.

Methods and results In this single-centre observational study, 3669 patients with acute ischaemic stroke were retrospectively analysed regarding AF status and medication immediately before admission. Using multivariable regression, we analysed the association of pre-admission anticoagulation with severe stroke (National Institutes of Health Stroke Scale score ≥ 11) on admission and poor outcome at discharge (modified Rankin scale score > 2). Before the index stroke, 655 patients had known AF and a CHA_2DS_2-VASc score ≥ 2. While 325 (49.6%) patients were anticoagulated, 159 (24.3%) were prescribed a NOAC and 75 (11.5%) phenprocoumon patients had an INR ≥ 2 on admission. Compared with AF patients without medical stroke prevention, an INR ≥ 2 [OR 0.23 (95% CI 0.10–0.53)] or NOAC intake [OR 0.48 (95% CI 0.27–0.86)] were associated with a lower probability of severe stroke after adjustment for confounders, while an INR < 2 [OR 0.62 (95% CI 0.33–1.16)] was not. Adjusted odds ratios for poor functional outcome at hospital discharge were 0.47 (95% CI 0.27–0.84) for NOAC patients, 0.33 (95% CI 0.17–0.65) for INR ≥ 2 and 0.61 (95% CI 0.32–1.16) for INR < 2.

Conclusion NOAC intake before stroke did reduce the probability of severe stroke on hospital admission and poor functional outcome at hospital discharge as similarly demonstrated for phenprocoumon patients with an INR ≥ 2 on admission.

Keywords Atrial fibrillation • Ischaemic stroke • Morbidity • NOAC (Non-vitamin K oral anticoagulants) • Stroke aetiology

Introduction

Non-valvular atrial fibrillation (AF) is the most common cardiac arrhythmia worldwide. AF increases the individual stroke risk about four- to five-fold, and at least 15% of all ischaemic strokes are caused by AF. Oral anticoagulation significantly reduces the risk of (recurrent) stroke in patients with AF, and relevant guidelines strongly recommend oral anticoagulation in AF patients with at least one additional risk factor for stroke.[1–3] Four phase III studies have demonstrated that non-vitamin K-dependent oral anticoagulants (NOACs) are at least equally effective to the vitamin K antagonist (VKA) warfarin with a median time in therapeutic range between 58

* Corresponding author. Tel: +49 30 450560663; fax: +49 30 450560979. *E-mail address*: georg.haeusler@charite.de

What's new?

- Despite the availability of non-vitamin K-dependent oral anticoagulants, there is a significant under-treatment in primary and secondary stroke prevention in patients with known atrial fibrillation and a CHA_2DS_2-VASc score ≥ 2 presenting with acute ischaemic stroke in a German university hospital.
- The intake of a non-vitamin K-dependent oral anticoagulant before stroke onset reduces the probability of severe stroke on hospital admission as well as poor functional outcome at hospital discharge, as similarly demonstrated for phenprocoumon treated patients with an international normalized ratio ≥ 2 on hospital admission.

and 68% in these trials.[4] However, the use of oral anticoagulants is restricted by contraindications such as renal failure or previous bleeds. In addition, the feared risk of bleeding leads to non-compliance with guideline recommendations.[5,6] Consecutively, only a subset of all acute ischaemic stroke patients with known AF before stroke is (sufficiently) anticoagulated when stroke occurs, as demonstrated in multiple observational studies.[7,8] Insufficient long-term persistence to VKAs or NOACs is another major problem in stroke patients.[9,10] While platelet inhibitors are a cornerstone of secondary stroke prevention in non-AF patients, they are no longer recommended by current guidelines for stroke prevention in AF patients.[1–3]

Stroke in patients with AF is more often disabling and associated with increased morbidity and mortality compared with stroke in patients without AF.[11] In addition to the reduction of stroke risk, the intake of VKA reduces stroke severity and improves long-term outcome if the international normalized ratio (INR) is within therapeutic range at stroke onset.[8,12] One could argue that there might be a similar effect of pre-admission NOAC intake on stroke-related morbidity and mortality but there is—besides a retrospective analysis including nine patients with NOAC intake before ischaemic stroke—no published analysis so far.[13,14] Interestingly, recently published experimental data showed a beneficial effect of rivaroxaban pretreatment on stroke severity in rats.[15] Consequently, we analysed this assumption in a cohort of stroke patients consecutively admitted at our department within 3 years.

Methods

Study design

This single-centre observational study was conducted at the Department of Neurology, Charité - Universitätsmedizin Berlin and approved by the local Ethics Committee (EA2/022/15). Medical records of 3669 patients consecutively admitted to the stroke unit of the Department of Neurology, Charité - Universitätsmedizin Berlin, Campus Benjamin Franklin, between 1 January 2013 and 31 December 2015 were retrospectively analysed. Patients suffering an ischaemic stroke or transient ischaemic attack (TIA) (labeled as 'index stroke') were identified by using relevant ICD-10 discharge diagnoses (I63.x; G45.x). All patients with ischaemic stroke or TIA and known AF before admission for their index stroke were included in the primary analysis. We did not include patients suffering from haemorrhagic stroke. The following information was assessed from medical records: demographic details, cardiovascular risk factors (e.g. atrial fibrillation, congestive heart failure, hypertension, diabetes mellitus, previous stroke or TIA, intracerebral haemorrhage or non-stroke vascular events), potential contraindications for oral anticoagulation (such as malignant tumours or epilepsy), CHA_2DS_2-VASc score before the index stroke, antithrombotic medication before admission, INR on admission, thrombin time, activated partial thromboplastin time (aPTT), iv thrombolysis or mechanical intervention, diagnostic results during the hospital stay (echocardiography, ultrasound of the brain-supplying arteries, brain imaging), stroke severity on admission according to the National Institutes of Health Stroke Scale (NIHSS) score as well as functional outcome at hospital discharge according to the modified Rankin Scale (mRS).[16–18] Severe stroke was defined as NIHSS ≥ 11 points.[8] Poor functional outcome was defined as mRS > 2 at hospital discharge.

Statistical analysis

The results are reported as frequencies and percentages for categorical variables. In the case of continuous variables, mean and standard deviation (SD) are reported for sufficiently normally distributed data ($|\text{skewness}| < 1$) or median and inter-quartile range (IQR) for quantitatively skewed variables. Differences regarding baseline parameters between patients with different pre-stroke antithrombotic medication were tested using either χ^2, Fisher's exact test, or Student's *t*-test for independent samples (*Table 1*). First, we tested overall differences between six cohorts using χ^2 test or one-way ANOVA (for age). In case of $P \leq 0.1$, we performed post-hoc exploratory tests for the NOAC cohort vs. other cohorts. A two sided significance-level of $\alpha = 0.05$ was applied. Severe stroke (NIHSS ≥ 11) and poor functional outcome (mRS > 2) were the main outcomes. *P*-values testing different characteristics with regard to these outcomes were age-adjusted using binary logistic regression models (Supplementary material online, *Table S2*). In multiple logistic regression, associations between antithrombotic treatment and stroke severity at admission and functional outcome at discharge were tested after adjustment for age, sex, diabetes mellitus, previous stroke, coronary artery disease, congestive heart failure, peripheral artery disease, renal insufficiency, epilepsy, and malignant tumour (*Table 2*). In addition, endovascular treatment was added to the model regarding the functional outcome at hospital discharge. Stroke severity and iv thrombolysis however are affected by oral anticoagulation at stroke onset and have an impact on functional outcome. Instead of being mere confounders, they are factors on the 'causal pathway' from anticoagulation treatment to functional outcome at discharge and cannot simply be adjusted for in multiple regression analysis.[19] Therefore, we performed a structural equation analysis to evaluate the causal relationship between anticoagulatory treatment, NIHSS score on admission as well as iv thrombolysis and functional outcome at hospital discharge (Supplementary material online, *Figure S1*). Odds ratios (OR) with 95% confidence intervals (CI) are reported. Despite of comparably small groups, we performed a sensitivity analysis comparing NOAC patients with or without altered routine anticoagulation tests to those patients without medical stroke prevention. Data were analysed using SPSS statistics 23 and SPSS AMOS 24 (IBM Corp., Armonk, NY, USA).

Results

Out of 3669 patients suffering from acute ischaemic stroke or TIA, 671 (18.3%) had a medical history of AF before index stroke. Sixteen patients had a CHA_2DS_2-VASc score < 2 and were not included in further analysis because anticoagulation was not (definitively)

Table 1 Baseline characteristics in 655 patients with known AF, acute ischaemic stroke or TIA and a CHA_2DS_2-VASc score ≥ 2

	$\sum$ ($n = 655$)	NOAC ($n = 159$)	VKA INR$\geq$2 ($n = 75$)	VKA INR<2 ($n = 91$)	Platelet inhibitor ($n = 206$)	No med. ($n = 99$)	Others ($n = 25$)	P (over all)	P NOAC vs. INR$\geq$2	P NOAC vs. INR<2	P NOAC vs. Platelet inhibitor	P NOAC vs. No med.
Age in years; mean (SD)	80 (9)	79 (8)	79 (7)	80 (7)	82 (9)	80 (11)	80 (7)	0.011	0.438	0.752	0.003	0.664
Female sex; *n* (%)	363 (55.4)	74 (46.5)	35 (46.7)	60 (65.9)	122 (59.2)	59 (59.6)	13 (52.0)	0.019	0.986	0.003	0.016	0.041
Previous stroke/TIA; *n* (%)	250 (38.2)	80 (50.3)	23 (30.7)	32 (35.4)	73 (35.4)	30 (30.3)	12 (48.0)	0.006	0.005	0.020	0.004	0.002
Diabetes; *n* (%)	188 (28.7)	56 (35.2)	22 (29.3)	27 (29.7)	58 (28.2)	21 (21.2)	4 (16.0)	0.152				
Hypertension[a]; *n* (%)	599 (91.6)	145 (91.2)	72 (96.0)	85 (93.4)	191 (92.7)	84 (85.7)	22 (88.0)	0.188				
Heart failure; *n* (%)	139 (21.2)	23 (14.5)	9 (12.0)	20 (22.0)	61 (29.6)	22 (22.2)	4 (16.0)	0.004	0.608	0.130	0.001	0.110
Coronary artery disease; *n* (%)	166 (25.3)	48 (30.2)	17 (22.7)	21 (23.1)	58 (28.2)	15 (15.2)	7 (28.0)	0.113				
Peripheral artery disease; *n* (%)	53 (8.1)	15 (9.4)	5 (6.7)	8 (8.8)	17 (8.3)	6 (6.1)	2 (8.0)	0.944				
Renal insufficiency; *n* (%)	150 (22.9)	37 (23.3)	10 (13.3)	15 (16.5)	56 (27.2)	25 (25.3)	7 (28.0)	0.116				
Malignant tumour; *n* (%)	94 (14.4)	22 (13.8)	9 (12.0)	14 (15.4)	32 (15.5)	8 (8.1)	9 (36.0)	0.020	0.699	0.737	0.651	0.161
Epilepsy; *n* (%)	24 (3.7)	8 (5.0)	2 (2.7)	5 (5.5)	6 (2.9)	2 (2.0)	1 (4.0)	0.664				
Thrombolysis; *n* (%)	112 (17.1)	6 (3.8)[b]	–	16 (17.6)	52 (25.2)	36 (36.4)	2 (8.0)	<0.001	0.181	<0.001	<0.001	<0.001
Endovascular treatment; *n* (%)	31 (4.7)	6 (3.8)	1 (1.3)	8 (8.8)	12 (5.8)	3 (3.0)	1 (4.0)	0.262				
Admission NIHSS $\geq$ 11; *n* (%)	190 (29.0)	35 (22.0)	9 (12.0)	27 (29.7)	74 (35.9)	40 (40.4)	5 (20.0)	<0.001	0.067	0.177	0.004	0.002
Admission mRS > 2; *n* (%)	409 (62.4)	86 (54.1)	33 (44.0)	64 (70.3)	142 (68.9)	72 (72.7)	12 (48.0)	<0.001	0.150	0.012	0.004	0.003
In-hospital stay in days; median (IQR)	5 (4–8)	5 (4–7)	5 (4–7)	6 (4–8)	6 (4–7)	6 (4–8)	6 (5–10)	0.106				
In-hospital mortality; *n* (%)	43 (6.6)	7 (4.4)	3 (4.0)	5 (5.5)	17 (8.3)	9 (9.1)	2 (8.0)	0.487				

Cohorts are separated according to medical stroke prevention before the index stroke.
Overall test: χ^2 or Fisher's exact test/one way ANOVA for age, Kruskal–Wallis-Test for hospital stay.
[a]Missing values: $n = 3$.
[b]Individualized treatment decision after obtaining informed consent in four patients with normal PTT and INR. NOAC intake <24 h was not known at the time of treatment in two patients.

Table 2 **Adjusted[a] odds ratios and 95% CI for antithrombotic medication taken prior to admission with regard to severe stroke on hospital admission (NIHSS ≥ 11) and poor functional outcome at hospital discharge (mRS > 2) in 655 AF patients with acute ischaemic stroke or TIA and a CHA_2DS_2-VASc score ≥2 before admission**

	NIHSS ≥ 11 On admission	mRS > 2 At discharge
Nagelkerke R^2	0.14	0.23
No antithrombotic medication	1 [reference]	1 [reference]
Platelet inhibitors	0.80 (0.47–1.34)	0.82 (0.47–1.42)
Heparin, low-dose	0.41 (0.12–1.41)	0.39 (0.13–1.18)
VKA		
INR < 2	0.62 (0.33–1.16)	0.61 (0.32–1.16)
INR ≥ 2	0.23 (0.10–0.53)	0.33 (0.17–0.65)
NOAC	0.48 (0.27–0.86)	0.47 (0.27–0.84)
Other anticoagulants[b]	0.59 (0.06–5.76)	0.66 (0.10–4.52)

[a]Multiple logistic regression analysis was adjusted for: age, sex, diabetes mellitus, previous stroke, coronary artery disease, congestive heart failure, peripheral artery disease, renal insufficiency, epilepsy, malignant tumour, and additionally for endovascular treatment in the model for mRS > 2 at discharge (Supplementary material online, *Table S2*).
[b]Including fondaparinux ($n = 3$) or therapeutic dose heparin iv ($n = 2$).

indicated before the index stroke. Baseline characteristics of 655 patients with known AF and a CHA_2DS_2-VASc score ≥ 2 before the index stroke are depicted in *Table 1*. In total, 530 (80.9%) out of 655 patients (mean age 80 years; 55.4% female) suffered an ischaemic stroke and 125 (19.1%) patients had a TIA. Median NIHSS score was 5 (IQR 1–12) on admission, and 6 (IQR 3–14) after excluding TIA patients. Forty-three (6.6%) of 655 stroke patients with AF died during the in-hospital stay [median 5 days (IQR 4–8)].

Medical stroke prevention before admission in patients with known AF before index stroke

From all 655 patients with known AF and a CHA_2DS_2-VASc score ≥ 2 before the index stroke, 325 (49.6%) received oral anticoagulation before admission [VKA phenprocoumon $n = 166$ (25.3%), $n = 75$ (11.5%) with INR ≥ 2 on admission; NOAC $n = 159$ (24.3%)]. Forty-seven (14.5%) of 325 anticoagulated patients also took a platelet inhibitor (+VKA $n = 19$; +NOAC $n = 28$). Three patients received fondaparinux and two patients therapeutic-dose intravenous heparin. Furthermore, 206 (31.5%) out of 655 patients received a platelet inhibitor (dual therapy $n = 20$). While 20 (3.1%) patients had low-dose heparin, 99 (15.1%) patients had no antithrombotic medication (*Table 1*). Comparing patient cohorts receiving a NOAC, VKA, platelet inhibitor or no medical stroke prevention to each other, significant differences were observed regarding age, gender, previous stroke as well as co-existing heart failure, thrombolysis on admission, NIHSS as well as mRS on admission (*Table 1*). A reduced dose of rivaroxaban as well as apixaban was prescribed in 61% and 49% of the respective patient cohort (Supplementary material online, *Table S1*).

Impact of oral anticoagulants on stroke severity on admission

On hospital admission, 190 (29.0%) out of 655 patients with known AF and a CHA_2DS_2-VASc score ≥ 2 before the index stroke had a NIHSS ≥ 11 indicating severe stroke. In bivariate analysis, old age, female sex, co-existing heart failure, coronary artery disease, and malignant tumour were associated with a higher probability of severe stroke on admission (Supplementary material online, *Table S2*). After adjustment for confounders, VKA intake resulting in an INR ≥ 2 on admission [OR 0.23 (95% CI 0.10–0.53)] as well as NOAC intake [OR 0.48 (95% CI 0.27–0.86)] were inversely associated with severe stroke on admission when compared with patients without antithrombotic medication at stroke onset (*Table 2*).

Impact of oral anticoagulants on functional outcome at hospital discharge

Comparing patient cohorts receiving different therapeutic regimens before admission, significant differences were observed regarding the rate of intravenous thrombolysis and NIHSS score on admission but not regarding the duration of the in-hospital stay (*Table 1*). At discharge, 342 (52.2%) out of 655 patients with known AF and a CHA_2DS_2-VASc score ≥ 2 before the index stroke had a mRS > 2 indicating poor functional outcome. In bivariate analysis, old age, co-existing diabetes, heart failure, and higher NIHSS score on admission were associated with poor functional outcome (Supplementary material online, *Table S2*). In multivariable analysis, VKA intake resulting in an INR ≥ 2 on admission [OR 0.33 (95% CI 0.17–0.64)] as well as NOAC intake [OR 0.49 (95% CI 0.28–0.86)] were inversely associated with poor functional outcome at hospital discharge when compared with patients without antithrombotic medication at stroke onset (*Table 2*).

Adherence regarding NOAC intake before admission

According to documented patient statements, NOAC intake was not discontinued immediately before admission in 159 AF patients. Patient-reported daily dose and the results of routine coagulation tests (INR, aPTT, or thrombin time) on admission are depicted in Supplementary material online, *Table S2*. Overall, 90 (56.6%) NOAC patients had altered routine coagulation tests indicating an anticoagulatory effect at stroke onset. Compared with patients without antithrombotic medication, NOAC patients with altered coagulation tests had a significantly lower rate of severe stroke (NIHSS ≥ 11) on admission (18.9% vs. 40.4%; OR 0.41 (95% CI 0.20–0.83) adjusted for age, sex, coronary artery disease, malignant tumour, peripheral artery disease, heart failure), while NOAC patients without altered coagulation tests had a non-significant lower rate of severe stroke (26.1%; adjusted OR 0.62 (95% CI 0.31–1.25).

Discussion

One of the major findings of this study is that only half of the patients with known AF and a CHA_2DS_2-VASc score ≥ 2 before stroke were

taking oral anticoagulation despite given indication. This finding underlines the present shortcomings in primary and secondary stroke prevention in AF patients and furthermore demonstrates subsequent complications. However, we analysed only AF patients with acute ischaemic stroke; therefore, we cannot draw conclusions on the quality of stroke prevention in AF patients in the general population.

Compared with AF patients without antithrombotic medication before stroke (*Table 2*), self-reported NOAC intake pre-admission lowered the probability of severe ischaemic stroke on hospital admission, as similarly observed for phenprocoumon patients with an INR ≥ 2 on admission. In accordance with previous publications, there was no significant effect of VKA intake with an INR < 2 or the intake of platelet inhibitors on stroke severity on admission.[8,20] NOAC intake also lowered the probability of worse functional outcome at hospital discharge (*Table 2*), despite of a higher rate of previous stroke and a lower rate of thrombolysis in patients taking a NOAC when compared with AF patients without antithrombotic medication (*Table 1*). A similar effect on stroke severity at hospital discharge was observed in VKA patients with an INR ≥ 2 on admission (*Table 2*). Adjusted for various confounders, the multiple relations of stroke severity on admission, thrombolysis as well as endovascular treatment on functional outcome at hospital discharge are depicted in the Supplementary material online, *Figure S1*. As demonstrated, the NIHSS score on admission significantly impacts on the mRS score at discharge. Moreover, intake of phenprocoumon or NOAC was inversely related to stroke severity on admission, as indicated by the negative estimates.

NOACs are effective in primary and secondary stroke prevention without need for routine coagulation monitoring.[4] However, a non-temporal correlation was reported between (single) plasma concentrations of dabigatran and edoxaban and cerebrovascular events during follow-up of the respective phase III clinical trials.[21,22] Just recently, a single-centre case series including 19 patients admitted for acute stroke while taking dabigatran demonstrated that plasma concentrations of dabigatran were higher in four patients with intracerebral haemorrhage compared with 15 patients with ischaemic stroke.[23] Because NOAC plasma concentrations on admission or measurements of calibrated anti-Xa activity were not available in our stroke cohort, coagulation tests on hospital admission were analysed (as similarly reported in a German registry).[24] Despite uncertain sensitivity and specificity, these tests provide useful information to assess a residual anticoagulant effect of NOACs—in patients with abnormal results—indicating a recent intake.[25] Of note, NOAC patients with elevated routine coagulation tests had a significantly lower probability of severe stroke when compared to patients without antithrombotic medication on admission. This was not the case for NOAC patients without elevated routine coagulation tests. With regard to the published phase III randomized trials, the reduced dose of rivaroxaban as well as apixaban was more often prescribed in our stroke cohort (Supplementary material online, *Table S1*).

Limitations of the present study

Beside the reported strengths, our study has weaknesses that mitigate the validity of its results. First, this is a retrospective single-centre analysis and we cannot exclude that undocumented factors have influenced the physicians' choice of medical stroke prevention in an individual patient pre-stroke. Second, there are limitations in terms of statistical power to the various comparisons due to comparably small patient subgroups. Third, there were significant differences between patient subgroups regarding baseline characteristics and acute stroke treatment. Despite statistical adjustment, residual bias may still be present. Fourth, we were unable to assess the adherence to NOAC intake and the actual anticoagulatory effect at the time of stroke onset in more detail because specific tests like calibrated anti-Xa activity are not part of clinical routine so far.[24] We addressed this issue by comparing NOAC patients with and without altered routine coagulation tests to those patients without medical stroke prevention. Fifth, due to retrospective data assessment we were unable to assess the impact of pre-hospital time in therapeutic range (TTR) on stroke severity. Since the half-life of phenprocoumon is much longer compared to warfarin, we believe that INR on admission is sufficient to assess the quality of anticoagulation in the last week before stroke.[26] Finally, we missed an additional follow-up 3 months after stroke that would have strengthened our results. Therefore, our findings have to be validated in larger cohorts of stroke patients with known AF as suggested previously.[13]

Supplementary material

Supplementary material is available at *Europace* online.

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Erratum

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Erratum to: Occupational radiation exposure in the electrophysiology laboratory with a focus on personnel with reproductive potential and during pregnancy: A European Heart Rhythm Association (EHRA) consensus document endorsed by the Heart rhythm Society (HRS) [*Europace* 2017;19:1909–1922].

In 10.1093/europace/eux252, Tatjana Potpara had not been mentioned among the members of the ESC Scientific Document Group, and another member had been added erroneously. This has now been corrected online. The Editors apologise for this error.