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Impact of pre-admission treatment with non-vitamin K oral anticoagulants on stroke severity in patients with acute ischemic stroke

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Abstract

Background Non-vitamin K antagonist oral anticoagulants (NOACs) have gained increasing importance for stroke prevention in patients with non-valvular atrial fibrillation (AF). With changing prescription practice, among other factors, clinicians can expect to see rising numbers of patients with ischemic stroke and pre-existing NOAC therapy. Few data exist regarding a potential impact of NOAC on stroke severity and outcome.

Aims To evaluate the impact of pre-admission NOAC therapy on ischemic stroke severity.

Methods Retrospective analysis of medical data of 376 patients with newly detected AF or known AF with either no pre-admission oral anticoagulation (n = 277) or existing NOAC therapy (n = 99; Apixaban, n = 33, Dabigatran, n = 16; Edoxaban, n = 1; Rivaroxaban, n = 49) consecutively admitted for acute ischemic stroke between January 2015 and December 2016.

Results Patients with pre-admission NOAC had significantly more often experienced a prior stroke than patients not on NOAC therapy (45.5 vs. 18.4%, $p < 0.001$) and were significantly more frequently non-smokers (1.0 vs. 7.2%, $p = 0.021$). Significantly more patients without pre-admission NOAC received thrombolysis (33.8 vs. 8.1%, $p < 0.001$). Pre-admission NOAC therapy was associated with significantly lower NIHSS and mRS scores upon admission (median NIHSS score 6 vs. 10, $p = 0.018$, median mRS score 4 vs. 5, $p = 0.035$) and trend-level lower NIHSS scores at discharge (median NIHSS score 3 vs. 5, $p = 0.057$). There were no differences regarding the frequency of symptomatic intracerebral hemorrhage between NOAC and non-NOAC patients ($p > 0.05$).

Conclusions We report a positive impact of pre-admission NOAC on ischemic stroke severity, which is particularly remarkable in light of the increased prevalence of prior stroke and lower rates of thrombolysis in this patient population.

Keywords Atrial fibrillation · NOAC · Secondary prevention · Neurology · Ischemic stroke · Stroke severity

Introduction

Non-valvular atrial fibrillation (AF) is a relevant risk factor for ischemic stroke, accounting for 15–20% of all strokes [1], and cardioembolic strokes are associated with more severe deficits than strokes of different etiology [2]. Vitamin K antagonists (VKA) have long been the foundation of therapy for patients with AF, however, due to their narrow therapeutic window necessitating frequent monitoring and food and drug interactions, adherence is often problematic [3]. The introduction of four non-vitamin K antagonist oral anticoagulants (NOACs) in recent years has thus been a welcome addition to the therapeutic arsenal for primary and secondary stroke prevention in AF patients. With equal or superior safety and efficacy compared to VKAs [4] and no need for interaction monitoring, prescription and use of NOACs has risen substantially, accounting for more than half of new prescriptions for AF [5, 6]. While the annual rate for ischemic strokes or systemic embolic events under NOAC therapy was 1–2% in large phase III clinical trials [7–10], clinicians can expect to see increasing numbers of patients with ischemic stroke taking NOACs in the future

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due to prescription changes, increased prevalence of AF [11] and potentially extended indications for NOAC use [12].

While VKA intake with international normalized ratio values within the therapeutic range is associated with improved functional outcome in patients suffering from ischemic stroke [13–15], fewer data exist regarding a potential impact of pre-admission NOAC therapy on stroke severity. Recent studies suggest a positive effect [16–18].

Aims

We sought to further elaborate on the potential impact of pre-admission NOAC therapy on stroke severity and hypothesize that patients on NOAC therapy suffering ischemic stroke present with less severe neurological deficits compared to patients not taking NOACs.

Methods

We retrospectively analyzed medical data of 376 patients with newly detected or known AF with either no pre-admission oral anticoagulation, i.e. neither NOAC nor VKA (henceforth for reasons of simplicity referred to as non-NOAC patients), or existing NOAC therapy (henceforth referred to as NOAC patients) who were consecutively admitted to the stroke unit of the University Medical Centre, Mannheim, Germany, for acute ischemic stroke between January 2015 and December 2016.

The study was approved by the local ethics committee. Patients taking VKA and patients with hemorrhagic strokes were not included in the analysis. The following information was obtained from medical records: demographics, vascular risk factors (arterial hypertension, diabetes mellitus, previous stroke, previous myocardial infarction, smoking status on admission), antiplatelet and NOAC therapy upon admission, stroke severity on admission and discharge assessed by the National Institute of Health Stroke Scale (NIHSS), functional outcome at discharge according to the modified Rankin Scale (mRS). Stroke severity was categorized according to the NIHSS scale as minor (0–4 points), moderate (5–15 points), moderate-to-severe (16–20 points) and severe (> 20 points). Hemorrhagic events, i.e. hemorrhagic transformation and parenchymal hemorrhage, were assessed on the basis of imaging on admission and classified using ECASS radiological definitions [19]: HI I equals small petechiae located at the margins of the infarcted area, HI II is defined as confluent petechial bleeding within the infarcted area, but without any space-occupying effect, PH I is defined as blood clot not exceeding 30% of the infarcted area with mild space-occupying effect, and PH II subsumes dense blood clot(s) in more than 30% of the infarct volume with significant space-occupying effect. In addition, symptomatic intracranial hemorrhage (sICH) was assessed on the basis of clinically indicated follow-up imaging and defined according to ECASS III as any apparently extravascular intracranial blood associated with clinical deterioration of at least four NIHSS points, or that led to death and was the predominant cause of neurological deterioration [20]. Large vessel occlusion was defined as occlusion of any of the following: common carotid artery, internal carotid artery, basilar artery or M1 segment of the medial cerebral artery. Medium-to-large vessel occlusion was defined as large vessel occlusion or occlusion of any of the following: M2 segment of the medial cerebral artery, P1 and P2 segments of the posterior cerebral artery, or A1 and A2 segments of anterior cerebral artery determined by either ultrasound, CT angiography, MR angiography, or a combination thereof.

Statistical analysis was performed with IBM SPSS Statistics version 22.0. The distribution of categorial variables between both groups was compared by Chi2-Tests and Fisher's exact test in case of small cell sizes. Group comparisons of ordinal data were assessed using Mann–Whitney-U-Tests and group comparisons of metric data were assessed using independent samples T-Tests. P-values of <0.05 were defined as indicating statistical significance.

Results

Demographics

Baseline characteristics of patients are summarized in Table 1. There were no significant differences between patients with pre-admission NOAC therapy and patients without anticoagulation regarding age, gender, pre-admission modified Rankin scale as well as pre-existing dementia. Patients with pre-admission NOAC had significantly more often experienced a prior stroke than patients not on NOAC therapy (45.5 vs. 18.4%, $p<0.001$).

Regarding vascular risk factors, there were no relevant differences between the patient populations except for smoking status on admission, with NOAC patients being significantly more frequently non-smokers (1.0 vs. 7.2%, $p=0.021$). However, NIHSS scores at admission did not differ between smokers and non-smokers ($p=0.52$).

Atrial fibrillation and anticoagulation

Atrial fibrillation was newly detected in 155/376 (41.2%) patients, and AF was known in 221. Of those with known atrial fibrillation, 99/221 (44.8%) were taking NOAC upon admission. Of these, 66 (66.7%) received NOAC in the dosage recommended according to the summary of medicinal product characteristics. Of those patients with

Table 1 Characteristics of patients with cardioembolic stroke

	Non-NOAC (n = 277)	NOAC (n = 99)	p
Age (years; mean, SD)	79.4 (9.0)	79.2 (6.9)	0.817
Gender (male; n, %)	126 (45.5)	47 (47.5)	0.814
Cardiovascular risk profile			
Hypertension (n, %)	237 (85.6)	86 (86.9)	0.867
Diabetes (n, %)	88 (31.8)	28 (28.3)	0.612
Dyslipidemia (n, %)	75 (27.1)	30 (30.3)	0.602
Coronary heart disease (n, %)	65 (23.5)	33 (33.3)	0.062
Previous myocardial infarction (n, %)	29 (10.5)	17 (17.2)	0.106
Previous stroke (n, %)	51 (18.4)	45 (45.5)	*< 0.001*
Current smoker (n, %)	20 (7.2)	1 (1.0)	*0.021*
CHA_2D_2S-Vasc-Score (median)	4	5	*0.0012*
Morbidity			
Dementia (n, %)	52 (18.8)	17 (17.2)	0.765
Pre-mRS (median, min–max)	1 (0–2)	1 (0–2)	0.948
Medication			
Antiplatelet (n, %)	123 (44.4)	12 (12.1)	*< 0.001*
NOAC:			
Dabigatran (n, %)		16 (16.2)	
Rivaroxaban (n, %)		49 (49.5)	
Apixaban (n, %)		33 (33.3)	
Edoxaban (n, %)		1 (1.0)	
NOAC subtherapeutic dose (n, %)		33 (33.3)	
Acute stroke treatment			
iv-thrombolysis (n, %)	93 (33.8)	8 (8.1)	*< 0.001*
Thrombectomy (n, %)	30 (10.8)	10 (10.1)	0.84
Study medication (n, %)	2 (0.7)	0 (0.0)	
NIHSS and mRS scores			
Admission NIHSS (median, min–max)	10 (0–38)	6 (0–30)	*0.018*
Discharge NIHSS (median, min–max)	5 (0–42)	3 (0–42)	0.057
Admission mRS (median, min–max)	5 (0–5)	4 (0–5)	*0.035*
Discharge mRS (median, min–max)	4 (0–6)	4 (0–6)	0.132

Italic values indicate statistical significance

known AF but no NOAC intake, 64/122 (52.5%) were taking antiplatelet drugs. Twelve out of 99 patients taking NOAC (12.1%) additionally received antiplatelet therapy (Fig. 1). CHA_2DS_2VASc-Scores were significantly higher in patients with pre-admission NOAC than in patients without prior anticoagulation (median 5 vs. 4, p = 0.0012). There was no association between CHA_2DS_2VASc scores and initial stroke severity (p = 0.21). Out of 122 AF patients not on anticoagulation, 115 (94.3%) should have been anticoagulated on the basis of a CHA_2DS_2VASc score ≥ 2 but were not. There was a trend of these patients to be older than NOAC patients (81.3 vs. 78.1 years, p = 0.08). Sixty-four (52.5%) of this group received antiplatelet medication.

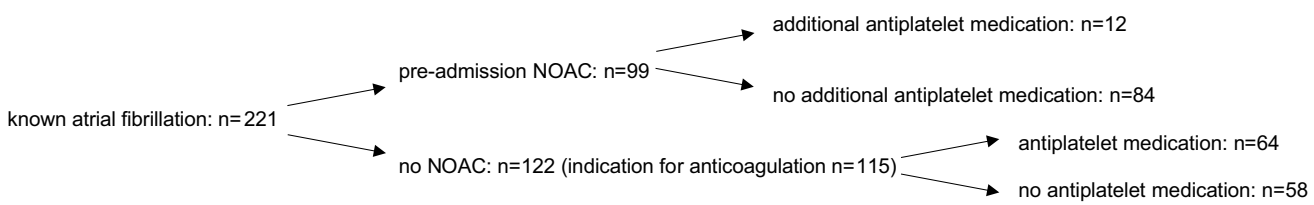

Fig. 1 NOAC and antiplatelet medication in patients with known AF

Stroke severity and outcome

Patients with prior NOAC therapy had significantly lower NIHSS scores upon admission (median NIHSS score 6 vs. 10, p = 0.018) with a trend for lower NIHSS scores for NOAC patients at discharge (median NIHSS score 3 vs. 5, p = 0.057). In addition, NOAC patients had lower mRS scores on admission (4 vs. 5, p = 0.035). NOAC patients were significantly more often affected by minor strokes than non-NOAC patients (45.5 vs. 28.5%, p = 0.003), and significantly less often by moderate-to-severe strokes (3.0 vs. 15.9%, p = 0.001). There were no differences between NOAC and non-NOAC patients regarding the frequency of moderate (30.3 vs. 36.5%, p = 0.33) and severe strokes (21.2 vs. 19.1%, p = 0.66). NOAC patients with a prior stroke displayed significantly lower NIHSS scores than non-NOAC patients with a prior stroke (median 7 vs. 13, p = 0.015). There was no significant difference in NIHSS scores at admission between patients receiving adequately dosed NOAC medication and patients with inadequate pre-admission NOAC dosage (median NIHSS score 5.5 vs. 7, p = 0.65).

NOAC patients receiving neither intravenous thrombolysis nor endovascular treatment showed a trend for lower NIHSS scores at discharge than non-NOAC patients not receiving thrombolysis or endovascular treatment (median NIHSS score 2 vs. 5, p = 0.071).

The difference between NIHSS scores upon admission and discharge, reflecting the extent of recovery, was not different between patients with pre-admission NOAC and patients without anticoagulation (p = 0.264). No difference between NOAC and non-NOAC patient regarding mRS on discharge was observed (median mRS 4, p = 0.132). Mortality, i.e. mRS of 6 upon discharge, was not different between NOAC and non-NOAC patients (14.1 vs. 13.0%, p = 0.734).

Treatment with intravenous thrombolysis and endovascular therapy

One hundred and twenty-six non-NOAC patients (45.5%) and 47 NOAC patients (47.5%) presented within the 4.5 h timeframe. Significantly more patients without pre-admission NOAC received thrombolysis (33.8 vs. 8.1%, p < 0.001). Regarding endovascular treatment, no difference was observed between pre-admission NOAC patients and patients without oral anticoagulation (10.1 vs. 10.8%, p = 0.84).

Occurrence of vessel occlusion and intracerebral hemorrhage

There was a trend towards more frequent occurrence of overall vessel occlusion in non-NOAC patients (33.9 vs. 24.2%, p = 0.079), but no difference in proximal vessel occlusion of internal carotid artery, M1 segment of medial cerebral artery or basilar artery (21.3 vs. 17.2%, p = 0.466).

There was no difference in the occurrence of any degree of parenchymal hemorrhage between NOAC and non-NOAC patients (7.1 vs. 7.6%, p = 1.00, see Table 2 for distribution of different degrees of parenchymal hemorrhage). In 253 patients, follow-up imaging was performed. Five sICH events were observed in non-NOAC patients, none in NOAC patients (p = 0.311). Of the five patients with sICH, three had received intravenous thrombolysis, one of these had also undergone endovascular treatment.

Discussion

We investigated whether pre-admission NOAC therapy in patients with AF and acute ischemic stroke impacted on stroke severity and functional outcome. We found more frequent minor strokes, a lower incidence of moderate-to-severe strokes and significantly lower NIHSS and mRS scores upon admission in patients with pre-existing NOAC therapy compared to patients without oral anticoagulation and trend-level lower NIHSS scores at discharge. Differences between NIHSS scores on admission and discharge were equal between the groups. Our data thus suggest that pre-admission NOAC therapy exerts a positive effect particularly on initial stroke severity but does not influence the extent of recovery. Our data partly corroborate recent studies [16–18] but contrast [21], where patients receiving NOAC or warfarin were found to experience more severe strokes than patients not on anticoagulation. Contrary to [16, 18], we did not find a significant difference regarding functional outcomes as assessed by discharge NIHSS and mRS scores; there were also no differences in in-hospital mortality between the groups. It may well be that a larger sample size would have pushed the trend-level NIHSS score

Table 2 Distribution of intraparenchymal hemorrhage in patients with and without pre-admission NOAC therapy

Degree of intraparenchymal hemorrhage	Non-NOAC (n = 277)	NOAC (n = 99)
No hemorrhage	256 (92.4%)	92 (92.9%)
HI I	7 (2.5%)	1 (1.0%)
HI II	11 (4.0%)	2 (2.0%)
PH I	0 (0%)	1 (1.0%)
PH II	3 (1.1%)	3 (3.0%)

HI I: small petechiae located at the margins of the infarcted area, HI II: confluent petechial bleeding within the infarcted area, no space-occupying effect, PH I: blood clot ≤ 30% of the infarcted area with mild space-occupying effect, PH II: dense blood clot(s) > 30% of the infarct volume with significant space-occupying effect

difference at discharge to significance. Moreover, standardized time-points of follow-up examinations may have drawn a different picture regarding longer-term differences in outcome between NOAC and non-NOAC patients.

While warfarin therapy appears to be associated with less severe strokes and better functional outcome only with INR levels within the therapeutic range [13, 22], no comparable information exists for the association of the intensity or therapeutic adequacy of pre-admission NOAC therapy and stroke severity. Since ischemic stroke occurs despite NOAC drug concentrations within peak ranges at the time of the stroke [23], there appears to be no straightforward relation, which may impede a more precise correlation of stroke severity with NOAC use. Our data reflect this issue: while minor and moderate-to-severe strokes occurred less frequently in NOAC patients, we found no difference in the occurrence of moderate and severe strokes between NOAC and non-NOAC patients. The accumulation of more data will be required for further clarification regarding quantitative aspects of NOAC therapy and its impact on stroke-associated deficits and outcomes.

It may be speculated that factors independent of pre-admission NOAC therapy contributed to the observation of lower NIHSS scores in NOAC patients. Prior stroke may have led to lifestyle modifications influencing our results: NOAC patients are more frequently non-smokers compared to patients not receiving oral anticoagulation therapy, and psychoeducative measures after a previous stroke may have contributed to this [24]. Moreover, dietary factors [25] and physical activity [26] not reflected in our data may have had a positive influence. We cannot exclude the possibility that etiologies other than cardioembolism, presumably leading to less severe deficits, caused some of the strokes in our study population.

We did not find significant differences in the incidence of intracerebral hemorrhage between NOAC and non-NOAC patients. NOACs are associated with a nearly 50% overall risk reduction in ICH rates [4], and a recent study showed no relevant differences in baseline ICH volume, hematoma expansion, 90-day mortality, and functional outcome in the wake of NOAC-ICH and VKA-ICH [27]. While there certainly is an increased bleeding risk compared to patients not taking anticoagulation, the lower rate of intravenous thrombolysis, a provoking factor for intracerebral hemorrhage, seems to be a partial counterweight. In line with this, of the five patients sufferings from sICH, three had undergone systemic thrombolysis and one of these three patients had also received endovascular treatment.

In an animal model of ischemic stroke with pre-treatment with either rivaroxaban or dabigatran, infarct size and functional deficit were significantly smaller in pre-treated animals [28, 29]. Reduced thrombus generation and thrombus formation, and subsequently smaller embolus size, as well as the attenuation of thrombin-induced neuroinflammation were suggested as underlying mechanisms. This is in line with experimental work on other thrombin inhibitors such as nafamostat mesilate, which reduced infarct volume and neurological deficits in a rat model of cerebral ischemia [30]. Accordingly, we found a trend towards less frequent overall vessel occlusion in NOAC patients but no difference in the frequency of large vessel occlusion. This is surprising since rivaroxaban and ximelagatran have been demonstrated to lead to a significant reduction of thrombus size *ex vivo* [31, 32]. Thrombus growth regulation is determined by a partly threshold-sensitive interplay [33] of soluble agonists and hemodynamics such as flow velocity [34]. Among others, the latter is influenced by left atrial appendage morphology, and certain configurations are more likely to impede blood flow [35] and in turn are associated with a higher incidence of cerebrovascular events [36]. It may well be that factors such as left atrial appendage morphology and function influenced thrombus formation in our patients. Since we did not find a significant difference between admission NIHSS scores of patients receiving NOAC in adequate dosages and those who did not—bearing in mind the complexity of the relationship between NOAC concentrations and occurrence of ischemic stroke [23]—it may be assumed that part of the positive impact of pre-admission NOAC therapy on initial stroke severity is mediated by a mechanism other than anticoagulatory activity per se.

A significantly smaller proportion of NOAC patients received intravenous thrombolysis despite admission to hospital within the first 4.5 h after onset of stroke symptoms. Our observation is in line with previous studies investigating this issue [16, 21] and reflects the ongoing uncertainty about acute stroke management in these patients. According to current AHA/ASA recommendations, thrombolysis can be administered if the patient did not take the anticoagulant in the 24 h preceding stroke and sensitive coagulation tests rule out the presence of anticoagulatory activity [37]. In a prospective observational registry study, the use of coagulation testing in patients suffering acute ischemic stroke taking NOAC was investigated [23]: standard coagulation tests, which are widely performed and readily available, were found to not accurately predict NOAC drug levels and anticoagulant activity. On the other hand, drug-specific tests were underutilized in the emergency scenario even in large hospitals. Experience and evidence is needed to specify and improve existing protocols, which currently yield inconsistent conclusions regarding the eligibility of NOAC patients for thrombolysis.

Endovascular therapy has been demonstrated to be safe and efficient in patients with large-vessel ischemic stroke [38] but patients taking oral anticoagulation were excluded in all trials. Previous studies did not find increased risk for sICH in patients undergoing endovascular therapy in a

setting of anticoagulation [39, 40] or in conditions of ineligibility for intravenous thrombolysis [41], and our study is in line with this. Hence, endovascular treatment as a therapeutic approach targeting the underlying acute pathology of stroke may be highly beneficial for these patients. Confirming prior work [16, 42], our results demonstrate underutilization of OAC use in spite of existing indication. As we studied exclusively patients with ischemic stroke, selection bias may not allow the generalization of our conclusions on the overall quality of stroke prevention in AF patients.

Our study is retrospective in character and thereby rests on the quality of existing documentation. Moreover, it lacks standardized follow-up examinations, which would have been useful in investigating longer-term functional outcome of NOAC and non-NOAC patients. We cannot exclude the possibility that undocumented factors impacted on the initiation of pre-admission oral anticoagulation in individual patients. Moreover, for NOAC patients we were unable to consistently evaluate anticoagulatory effects and plasma concentrations at the time of stroke as these tests are not part of the current emergency clinical routine. It would have been interesting to see whether an association of NOAC plasma concentration with stroke severity exists.

In sum, we report a positive impact of pre-admission NOAC therapy on the acute natural history of ischemic stroke, which is all the more remarkable in light of the increased prevalence of stroke prior to the index stroke, a direct consequence of the presence of AF necessitating NOAC therapy in the first place, and lower rates of thrombolysis in this patient population.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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